THE JOURNAL
of the American Medical Association
Published Under the Auspices of the Board of Trustees
VOL. 161, NO. 16 CHICAGO, ILLINOIS AUGUST 18, 1956
COPYRIGHT, 1956, BY AMERICAN MEDICAL ASSOCIATION

EFFICACY OF TRIVALENT ADENOVIRUS (APC) VACCINE IN NAVAL RECRUITS

PROGRESS REPORT

Joseph A. Bell, M.D., Bethesda, Md., Capt. Matthew J. Hantover (MC), U. S. Navy
Robert J. Heuner, M.D., Bethesda, Md., and Clayton G. Loosli, M.D., Chicago

• *The incidence of acute respiratory illnesses and the development of neutralizing antibodies are being studied in a comparison between a test group of 4,000 and contratest group of 12,000 naval recruits. Each member of the test group received a single 2-ml. intramuscular injection of a commercially prepared formaldehyde-inactivated APC (adenoidal-pharyngeal-conjunctival virus) vaccine, types 3, 4, and 7. The dosage was fixed by preliminary studies in which the vaccine was compared with a placebo, the cause of pain after injection was discovered and obviated, methods of study were tested, and the proportion of recruits to be vaccinated was decided. Laboratory data showed that the vaccine induced a substantial neutralizing antibody response to types 3, 4, and 7 adenovirus. The clinical data of the progress report, which covers only one-third of the experience, showed that the vaccine effected a substantial reduction, estimated at 50 to 75%, of the total expected febrile respiratory illnesses, which in this study were associated mainly with type 4 adenovirus.*

The inoculation of susceptible volunteers with laboratory-inactivated type 3 adenovirus (APC) vaccines has been shown to induce a neutralizing antibody response without untoward local or general reactions and to confer substantial protection against infection and illness induced (challenge) by type 3 virus.[1] (On May 25, 1956, investigators responsible for using the names adenoid degenerative (AD) viruses, adenoidal pharyngeal conjunctival (APC) viruses, respiratory illness (RI) viruses, and acute respiratory disease (ARD) viruses to designate a new group of respiratory viruses agreed to use henceforth the term "adenovirus" in lieu of former names.) Type 3 adenovirus causes acute febrile illness in civilians,[2] and types 3, 4, and 7 apparently cause acute febrile respiratory disease (ARD, febrile catarrh) in military recruits.[3] Since outbreaks of illness associated with all three virus types occurred in recruits at the United States Naval Training Center, Great Lakes, Ill.,[4] a cooperative study was undertaken to determine if type 3, 4, and 7 adenovirus vaccine would prevent naturally occurring acute respiratory disease in naval recruits.

In brief, the vaccine was a commercially prepared formaldehyde-inactivated, trivalent adenovirus vaccine, types 3, 4, and 7. It was given to a small group of men in a preliminary study on dosage and reaction on Dec. 19, 1955. The vaccine was then given to some 4,000 newly arrived recruits during the period from Jan. 11 to April 19, 1956, and the vaccinated recruits have been observed together with some 12,000 control recruits for the occurrence of acute respiratory illness. Although the laboratory, clinical, and epidemiological analyses are incomplete, the findings to date appear worthy of report. The vaccine induced a neutralizing antibody response to each of the three virus types without untoward local or general reactions and conferred substantial protection against acute febrile respiratory illness.

The vaccine was prepared commercially to make easier possible future reproduction for general use. Strains of types 3, 4, and 7 adenovirus, originally isolated and grown in monkey kidney cell cultures, were used.[5] Methods of mass virus culture and inactivation studies will be described elsewhere.[6] To assure identity and freedom from contamination with monkey renal or other "wild viruses," a rabbit serum containing homologous neutralizing antibodies was added to samples of each monovalent live virus pool and the mixture inoculated into monkey kidney and HeLa cell cultures. No cytopathogenic effect occurred. Inactivation was accomplished by adding a solution of formaldehyde to a final concentration of 0.25% and holding the suspension for 24 hours at 37 C in a shaking machine and then for one week or longer at 4 to 7 C. A sample of each monovalent inactivated virus pool was dialyzed and inoculated into monkey kidney and HeLa cell cultures, and no virus was detected. The formaldehyde solution was then partially neutralized with sodium bisulfite solution, reducing the formalin content to a final calculated concentration of 0.1%. The three pools were then mixed in equal proportions and packaged in 10-dose vials and maintained in a frozen state until used. Qualitative and quantitative tests for safety and sterility were carried out as prescribed for poliomyelitis vaccine,[7] with the single exception that monkey

inoculations were not done. Potency was assayed by inoculation of rabbits with each monovalent vaccine pool and the final trivalent product. Each pool and the final product induced a substantial neutralizing antibody response to each of the three virus types.[6] A second lot of vaccine was also commercially prepared in like manner for these studies, and the results of rabbit tests to assay potency were similar.

TABLE 1.—*Comparability of Neutralizing Antibody Tests of Aliquots of Same Serums in Different Laboratories Using Different Tissue Cell Cultures*

		Neutralizing Antibody Titers of Serums Tested at NAMRU-4 and							
		University of Chicago in HeLa Cell Cultures				NIH in Monkey Kidney Cell Cultures			
		<1:8	1:8	>1:8	Total	<1:8	1:8	>1:8	Total
Neutralizing Antibody Titers of Serums Tested at NAMRU-4 in HeLa Cell Cultures	<1:8	45	7	1	53	43	3	13	59
	1:8	5	5	6	16	3	3	15	21
	>1:8	29	37	84	150	5	1	155	161
Total		79	49	91	219	51	7	183	241
% ≧ "fourfold" difference*		30/219=14%				18/241=7%			

* Titer of <1:8 in one laboratory and >1:8 at the other.

Dosage and Procedure

The first part of this report concerns a preliminary study designed to determine what dose of vaccine would induce neutralizing antibodies to each of the three types of virus and to suggest the procedures to be used in subsequent mass protection studies. For the latter, it was desired (1) to know the status as regards neutralizing antibodies of arriving recruits so as to estimate the proportion that could be safely vaccinated without inducing "herd immunity" to an extent that might prevent the occurrence of disease in controls, (2) to assure that the commercially prepared product would not produce untoward local or general reactions, and (3) to test clinical, epidemiological, and laboratory methods to be used. To these ends, a total of 240 recruits in three training companies, who arrived at the training center between Dec. 1 and 11, were randomly distributed into six groups of about 40 men each. The distribution was made in such a manner that each company would have, as closely as possible, the same number of recruits in each group. Blood specimens were collected from all recruits on zero day, the day of vaccination, and on the 14th, 28th, and 37th days. Groups 1 and 3 received single doses of 1 and 2 ml. of vaccine, respectively, and 1 ml. of saline solution with formaldehyde at 14 days; groups 2 and 4 received two doses at 14-day intervals of 1 and 2 ml. of vaccine respectively; and groups 5 and 6 received two doses of 1 ml. of saline solution with formaldehyde. The vaccine and placebo were injected intramuscularly into the deltoid muscle, and no untoward reactions occurred except immediate pain, which lasted from two to five minutes. The pain was found to be due to too much residual formaldehyde and was entirely obviated in some 2,000 recruits subsequently vaccinated with the same vaccine lot after the formaldehyde concentration had been reduced to 0.025-0.05% with sodium bisulfite solution. In the second lot of vaccine, sodium bisulfite was added in an amount calculated to leave a residual concentration of 0.05% formalin, and this lot caused no pain on injection and no other untoward reaction.

All zero-day, 14-day, and 28-day serums available from each of the companies were tested at Naval Medical Research Unit No. 4 (NAMRU-4) in a single test with HeLa cell cultures for neutralizing antibodies to virus types 3, 4, and 7. The procedures were essentially the same as previously described, procedure 2[8] with modification. Tests were read 24 to 48 hours after virus controls first showed cytopathogenic changes 3 or 4+. A serum dilution was considered positive if ≦1+ cytopathogenic change occurred. Zero-day serums were tested at 1:4 dilution, and 14-day and 28-day serums were tested at 1:8 and 1:16 dilutions. In addition, with the results at NAMRU-4 unknown to the investigators, an aliquot sample of some of these serums was tested for neutralizing antibodies at the University of Chicago in HeLa cell cultures and another such sample of different serums was tested in monkey kidney cell cultures at the National Institutes of Health to observe the comparability of testing.

Serologic Results

The serologic results of the preliminary dosage study are shown in tables 1 and 2. Table 1 shows the comparability of the test results when aliquots of the same serum were tested at comparable dilutions to the same antigen in the different laboratories using different cell cultures. The test results compared better than anticipated, particularly in view of the fact that the end-point of the test is not absolute neutralization but depends on delay rather than prevention of cytopathogenic effect and in view of the likely differences in individual readings at the different laboratories. The monkey kidney cell test appeared more sensitive in detecting serum antibodies than the HeLa cell test. In all, the results of testing aliquot samples at two other laboratories confirmed the adequacy of the more extensive testing at NAMRU-4.

Table 2 shows the number and percentage of recruits developing neutralizing antibodies in the NAMRU-4 tests. It shows the results of testing paired zero-day and 14-day serums of the various vaccine groups 1 to 4 and the placebo groups 5 and 6 and also shows the totals for the vaccine and placebo groups in

TABLE 2.—*Recruits with Neutralizing Antibody Response in Zero-Day and Fourteen-Day and Zero-Day and Twenty-Eight-Day Serums by Vaccine and Placebo Groups*

Paired Serums	Inoculums: Study Group	Amount Vaccinated Ml.	Doses, No.	Recruits, No.	No. Developing Neutralizing Antibodies (Titer ≧1:8)/ No. with Zero-Day Neutralizing Antibodies (Titer ≦1:4): Type 3 No.	%	Type 4 No.	%	Type 7 No.	%
Zero and 14 days	1	1	1	41	8/16	50	15/28	54	11/18	61
	2	1	2	38	9/12	75	14/23	61	13/23	56
	3	2	1	37	8/13	62	12/22	55	12/18	67
	4	2	2	38	12/21	57	12/21	57	8/17	47
	1-4	Vaccine total		154	37/62	60	53/94	56	44/76	58
	5 and 6	Placebo total		71	8/31	26	13/50	26	5/39	13
Zero and 28 days	1-4	Vaccine total		154	42/62	68	75/94	80	48/76	63
	5 and 6	Placebo total		71	11/31	35	40/50	80	8/39	21

the zero-day and 28-day serums. Table 2 shows only changes in neutralizing antibody status from a zero-day titer $\leqq$1:4 (only two recruits had titers of 1:4) to a titer 1:8 or over; it does not show titer rises in recruits who had antibody titers >1:4 on zero-day. Previous studies showed that this change in antibody level represents a change from greater than 90% susceptibility to a moderate degree of immunity against a challenge-induced illness.[9] In the zero-day serums, the percentage of recruits in these three companies considered highly susceptible to illness caused by types 3, 4, or 7 may be computed from the totals in table 2. Such computations suggest that, of the 225 adequately tested, 93, 144, and 115 were susceptible to infection by types 3, 4, and 7 virus, respectively, i. e., 41%, 64%, and 51%. From these data, it would appear that, if a large proportion of arriving recruits were immunized, herd immunity might prevent outbreaks; hence, it was decided to vaccinate only 20% of arriving recruits.

Table 2 shows that, in the zero-day to 14-day serums, the percentage of recruits with antibody changes in the various vaccine dosage groups 1 to 4 was not significantly or consistently different. As compared with the placebo groups, however, the vaccine groups showed a significantly higher percentage of recruits with rises in neutralizing antibody titers to each of the three virus types. In the zero-day to 28-day serums, the totals show similar differences for types 3 and 7 antigen but not for type 4. It is noteworthy that type 4 adenovirus isolations were made from throat cultures collected from 11 recruits with acute febrile illness during the zero-day to 21-day period; no other virus type was isolated. Since types 3 and 7 were not isolated from such specimens, the rises in neutralizing antibodies to types 3 and 7 in the placebo groups were either heterotypic rises or due to undetected infection with these types. The prevalent natural infection with type 4 and the possible heterotypic responses preclude an accurate estimate of the amount of neutralizing antibody response caused by the vaccine per se, but it is clearly evident that the trivalent vaccine induced a significant neutralizing antibody response to each of the three virus types in a substantial number of recruits. Even though the data suggested no appreciable differences in the neutralizing antibody response to the various doses of vaccine given, a single 2-ml. dose was selected as most practical and desirable for the subsequent mass protection study.

The first commercial lot of vaccine was compared with the second similarly prepared lot on March 5, 1956, by inoculating a single 2-ml. dose of one or the other lot or a 2-ml. dose of placebo into men randomly assigned into three approximately equal groups from a company of 63 recruits. The paired zero-day and 14-day serums were tested for neutralizing antibodies at the University of Chicago. Of the 22 recruits in the placebo group, only one had a rise in titer for type 3 and none to type 4 or 7. This indicates slight or no concurrent natural infection with adenovirus types 3, 4, and 7 during the zero-day to 14-day period in this company. Of the 21 recruits who received the first vaccine lot, 9, 13, and 14 showed rises in neutralizing antibody titer to virus types 3, 4, and 7 respectively. Of the 20 who received the second vaccine lot, 10, 7, and 15 also showed rises to types 3, 4, and 7. Thus, serologic evidence in recruits indicates that the two separate commercially prepared lots both gave substantial and perhaps equivalent neutralizing antibody response.

Clinical Results

The second part of this report covers the crude experience with respiratory illness in vaccinated and nonvaccinated recruits of the first 91 companies participating in the mass protection study. It includes 5,260 men who entered observation between Jan. 11 and Feb. 13, 1956. This experience constitutes approximately the first third of the mass protection study, which will be reported in more detail when observations are completed. In general, recruits arrive almost daily at the training center in varying numbers. They are formed into companies of approximately 60 men each and routinely vaccinated against smallpox, typhoid, and tetanus. First doses are given on the third to fifth day after arrival, and recruits remain in training at the center for about nine weeks. In addition, recruits arriving Jan. 18 to April 23, who had histories of no penicillin sensitivity, received a single injection of 600,000 units of benzathine penicillin G (Bicillin) for prophylaxis against infection with Streptococcus organisms.

In 87 of the 91 companies, adenovirus vaccine was given intramuscularly in a single 2-ml. dose to a randomly selected 20% sample of recruits at the time of routine vaccinations. During the period from Jan. 11 to March 5, a study on influenza vaccine was also under way at the training center. Approximately one-half of all arriving recruits, selected at random, received aqueous polyvalent influenza vaccine, and the remainder received a saline solution with formaldehyde as a placebo control. In both studies recruits were randomly selected on the basis of their serial numbers. By such selections adenovirus vaccine was given to a near equal 20% of those receiving influenza vaccine and those receiving the placebo. Since many different inoculations were given to arriving recruits and since neither the observers nor the recruits knew who had received adenovirus vaccine, influenza vaccine, or control products, all recruits in the companies studied who did not receive adenovirus vaccine are adequate controls for the vaccinated group.

It was planned to give the study vaccine to only 20% of arriving recruits; however, by the time the study was under way, type 4 adenovirus was being isolated in some 40% of cases of acute respiratory illnesses reported at sick call. Since the vaccination of arriving recruits resulted in a relatively slow accumulation of vaccinees, all members of every 10th company formed from Feb. 7 to March 23 were vaccinated. It was felt that this would not greatly increase herd immunity of the entire recruit population, and it was hoped that eventual vaccination of 12 such companies in this manner might give evidence as to the effectiveness of the product in preventing infection in a whole company. The members of only 4 of the 91 companies included in this report were so vaccinated.

The observations for occurrence of acute respiratory illnesses were carried out by means of surveillance by NAMRU-4 of recruits reporting to sick call. Throat swabs for adenovirus and beta-hemolytic streptococci were collected from all recruits reporting to sick call with acute febrile respiratory illnesses (maximum temperature equal to or greater than 100 F [37.8 C]). In addition, special studies to be reported later were carried out wherein a random sample of recruits were visited in their barracks and had their temperatures taken, throat and blood specimens collected, and histories of new acute respiratory illness recorded. (A "new" respiratory illness was one in which the complaints, symptoms, or physical findings were chiefly directed to the respiratory tract and not obviously due to other known diseases, such as measles or mumps, and one that was new in the sense that the recruit had not reported to sick call for at least seven days.)

The adequacy of sampling procedures and the uniformity of observations were confirmed by the fact that rubella occurred in nearly equal percentages of vaccinated and nonvaccinated recruits in the 91 companies studied. Fifty-eight of 1,247 recruits (4.65%) reported to sick call with rubella in the vaccinated group, and 189 of 4,013 (4.71%) so reported in the nonvaccinated group. In all weeks proportions in each group were nearly equal.

TABLE 3.—*New Acute Respiratory Illnesses Reported at Sick Call by Vaccinated and Nonvaccinated Recruits in Ninety-One Companies Entering Study from Jan. 11 to Feb. 13, 1956*

		Illnesses During 1st 2 Wk.						Illnesses During 3rd to 9th Wk.					
		Nonhospital Admissions				Hospital Admissions		Nonhospital Admissions				Hospital Admissions	
		<100 F		≥100 F				<100 F		≥100 F			
Adenovirus Vaccine Group	Recruits No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Vaccinated	1,247	29	2.3	12	1	2	0.2	238	19.1	57	4.6	25	2
Nonvaccinated	4,013	71	1.8	60	1.5	26	0.6	818	20.4	389	9.7	227	5.7

During the weeks ending Jan. 14 to April 14, the admission rates for respiratory illnesses per thousand per week were unusually low. They ranged from 3.2 on Feb. 4, to 9 on March 24. Very few such illnesses were associated with streptococcic infection. These low rates at this season were in a large part attributed to the prophylaxis with benthazine penicillin G then in effect. Whether this would affect occurrence or reporting of respiratory illness due to virus is unknown. It is of interest that during early 1954, when no such prophylaxis was used, some 50% of acute febrile respiratory illnesses were associated with streptococcic infection and only some 25% of the remainder were attributable to adenovirus.[3d]

Table 3 shows the number and percentage of new respiratory illnesses reported at sick call by recruits in the first 91 companies entering the study between Jan. 11 and Feb. 13, 1956. These recruits have been observed throughout their nine-week training period. Since the vaccine could not be expected to be effective immediately after inoculation, the reported respiratory illnesses were arbitrarily separated into those occurring during the first two weeks after inoculation and those occurring during the remainder of the training period, i. e., in the third to ninth weeks. It is clearly evident from table 3 that, in weeks one and two and in weeks three to nine, there was no significant difference in the occurrence of minor afebrile respiratory illness in the vaccinated and nonvaccinated groups. On the other hand, in the third to ninth weeks and perhaps to a lesser extent in the first and second weeks, the vaccinated group had significantly fewer febrile illnesses and fewer hospital admissions than the nonvaccinated group. Although not shown in the table, this difference was uniformly present during each week of observation and was not materially altered when the members of the four entirely vaccinated companies were excluded. No outbreaks of influenza occurred, and there was no appreciable difference in either the total or the weekly percentage of reported illnesses among members of groups receiving and not receiving influenza vaccine.

The throat-swab specimens collected from recruits with acute febrile respiratory illness for virus isolation are stored at –65 C and are being tested in a random manner so as to minimize differences between tests. Since only about one-fifth of recruits in the companies studied were vaccinated, and since they experienced fewer illnesses than the nonvaccinated recruits, only 7 of the 88 specimens tested to date were from vaccinated recruits. Type 4 was isolated from 2 in the vaccinated group and from 21 in the nonvaccinated group; no other adenovirus type was recovered. This indicates that a substantial proportion of the febrile respiratory illnesses were due to type 4 virus and that illnesses attributable to types 3 and 7 were not prevalent during this period of observation. The comparatively low incidence of illness observed in the vaccine group shows the protection against illness caused by type 4 adenovirus. Since protection against a challenge-induced illness caused by type 3 virus has been demonstrated,[1] further studies are necessary to assess protection against illness caused by type 7.

Comment

A final assessment of the amount of protection conferred by the commercially prepared trivalent adenovirus vaccine must await completion of laboratory, clinical, and epidemiological analyses of the entire study group, which will be included in a later report. To date (table 3) it would appear that 50 to 70% of the total expected febrile respiratory illnesses were prevented by the vaccine, but this obviously will vary from time to time and from place to place depending primarily upon what proportion of total reported illnesses is caused by adenovirus of the types included in the vaccine. The vaccine used in this study was the first that has been prepared on a commercial scale, and perhaps more potent products will be developed.

It has been shown that type 3 adenovirus vaccine prevented infection as well as illness.[1] If this is true for types 4 and 7, it would appear likely that the vaccination of a substantial number of arriving recruits

might produce herd immunity sufficient to completely prevent outbreaks among recruits of respiratory illness due to adenoviruses.

Summary

A formaldehyde-inactivated adenovirus (APC) vaccine containing types 3, 4, and 7 has been commercially prepared and administered intramuscularly in a single 2-ml. dose to nearly 4,000 naval recruits without untoward local or general reactions. The vaccine induced a substantial neutralizing antibody response to each of the three types of virus contained in the vaccine. All evidence indicates that the vaccine induced a substantial reduction in the rate of occurrence of acute febrile respiratory illness associated with type 4 adenovirus. It would appear that the usual interference with military training routine resulting from acute febrile respiratory illnesses may be reduced by adenovirus vaccines.

National Institute of Allergy and Infectious Diseases (Dr. Bell).

This is a cooperative study conducted by Naval Medical Research Unit No. 4 (NAMRU-4) at U. S. Naval Training Center (USNTC), Great Lakes, Ill., the Laboratory of Infectious Diseases, National Institutes of Health (NIH), Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Md., and the Department of Preventive Medicine of the University of Chicago (U of C) at Chicago. Participating in this study were these persons: Directors—J. A. Bell, M.D. (NIH), M. J. Hantover, CAPT MC USN (NAMRU-4), R. J. Huebner, M.D. (NIH); Biometrician—W. T. Stille, M.S. (NAMRU-4); Clinician and Epidemiologist—J. E. Whiteside, CDR MC USN (NAMRU-4), and assistant, W. E. Pierce, HMC USN (NAMRU-4); Virology and Immunology—M. Friedman, Ph.D. (NAMRU-4), J. T. Grayston, M.D. (U of C), J. W. Hartley, M.S. (NIH), W. Pelon, Ph.D. (NAMRU-4), W. P. Rowe, M.D. (NIH), R. L. Woolridge, M.S. (NAMRU-4). Consultants included C. G. Looslie, M.D. (U of C), and T. G. Ward, M.D., Lobund Laboratories, Notre Dame University (formerly at Johns Hopkins University).

The opinions expressed herein are those of the authors and cannot be construed as reflecting the views of the Public Health Service at large of the Department of Health, Education, and Welfare, or of the Naval Service at large of the Department of Defense.

All seed virus used in this study was prepared at the National Institutes of Health. Live virus pools used were prepared by Parke, Davis & Company, Detroit, and Microbiological Associates, Inc., Bethesda, Md. Identity tests were done at the National Institutes of Health and inactivation at Parke, Davis & Company. Tests for inactivation, potency, and safety were carried out in duplicate at Parke, Davis & Company and the National Institutes of Health.

References

1. Huebner, R. J., and others: Studies of Adenoidal-Pharyngeal-Conjunctival Vaccines in Volunteers, J.A.M.A. **159**: 986-989 (Nov. 5) 1955.

2. Bell, J. A., and others: Pharyngoconjunctival Fever: Epidemiological Studies of Recently Recognized Disease Entity, J.A.M.A. **157**: 1083-1092 (March 26) 1955.

3. (*a*) Hilleman, M. R.; Werner, J. H.; Dascomb, H. E., and Butler, R. L.: Epidemiologic Investigations with Respiratory Disease Virus RI-67, Am. J. Pub. Health **45**: 203-210 (Feb.) 1955. (*b*) Ginsberg, H. S., and others: Etiologic Relationship of RI-67 Agent to "Acute Respiratory Diseases (ARD)," J. Clin. Invest. **34**: 820-831 (June) 1955. (*c*) Berge, T. O., and others: Etiology of Acute Respiratory Disease Among Service Personnel at Fort Ord, California, Am. J. Hyg. **62**: 283-294 (Nov.) 1955. (*d*) Rowe, W. P., and others: Study of Role of Adenoviruses (APC) in Acute Respiratory Infections in Navy Recruit Population, Am. J. Hyg., to be published.

4. Woolridge, R. L.; Grayston, J. T.; Whiteside, J. E., and Friedman, M.: Etiologic Studies of Febrile Respiratory Disease in Navy Recruits with Emphasis on APC Viruses, Fed. Proc. **15**: 340 (March, pt. 1) 1956.

5. Hartley, J. W.; Huebner, R. J., and Rowe, W. P.: Serial Propagation of Adenoviruses in Monkey Kidney Tissue Cultures, to be published.

6. Rightsel, W. A.; Dau, E., and McLean, I. W.: Studies on Experimental Polyvalent Adenovirus (APC) Vaccine, J. Immunol., to be published.

7. Minimum Requirements: Poliomyelitis Vaccine, 1st revision, U. S. Department of Health, Education, and Welfare, 1955.

8. Rowe, W. P., and others: Studies of Adenoidal-Pharyngeal-Conjunctival (APC) Group of Viruses, Am. J. of Hyg. **61**: 197-218 (March) 1955.

9. Bell, J. A., and others: Studies of Adenoviruses (APC) in Volunteers, Am. J. Pub. Health, to be published.

OBSERVATIONS ON ONE HUNDRED CASES OF HEATSTROKE

Martin G. Austin, M.D.
and
John W. Berry, M.D., St. Louis

• One hundred cases of heatstroke were selected for analysis from more than 1,000 hospital admissions during three exceptionally hot summers in a large city. These patients had the hot, dry skin that distinguishes heatstroke from other syndromes caused by high environmental temperatures. They also had symptoms referable to the central nervous system and temperatures usually exceeding 41.1 C (106 F). The greatest risk of life was in those patients with the severest central nervous system abnormalities; there were 12 deaths among the 53 patients who were comatos when admitted. Temperatures over 41.1 C, uremia, hypotension, and hyperpotassemia were also poor prognostic signs; all of the four patients with hyperpotassemia died. Treatment began with prompt total immersion and vigorous massage in an ice bath; this was followed by attention to cardiovascular status, electrolyte-fluid balance, oxygen requirements, and concurrent disease. Some of the data from laboratory studies on blood and cerebrospinal fluid supplied valuable therapeutic guidance, and a comparison with past mortality figures indicated that both prophylaxis and treatment have become more effective.

The summers of 1952, 1953, and 1954 were three of the six hottest summers in the past century and a quarter in St. Louis. Over 1,000 heat victims were observed in the receiving room of St. Louis City Hospital. Conditions of many were of a mild nature and did not require hospitalization; however, 178 patients had serious manifestations of the heat syndrome and were hospitalized for observation and treatment. This report is a review of 100 selected cases of heatstroke. Patients under the age of 12 years and those with heat exhaustion or prostration were excluded from this series.

The clinical pictures ascribed to high environmental temperatures have been well described by others. There are three fairly distinct syndromes that may arise from exposure to high environmental temperatures, although overlapping may occur. The first syndrome is heat cramps or salt depletion, manifested by muscle cramps, profuse sweating, polydipsia, and a normal temperature. This has been attributed to the marked loss of electrolytes as a result of profuse sweating. Heat exhaustion is characterized by profuse per-

From St. Louis University Medical School and St. Louis City Hospital.

spiration, pallor of the skin, low blood pressure, and a variable body temperature that is rarely elevated. The diagnosis of heatstroke depends upon (1) an adequate exposure to high environmental temperatures, (2) hyperpyrexia, over 106 F (41.1 C), (3) hot, dry skin, and (4) central nervous system signs. We have adhered to this definition except for the degree of hyperpyrexia. The variability of an absolute body temperature elevation over 106 F seems to us an artificial and arbitrary criterion. Ladell [1] has commented on a group of patients whose body temperatures were between 103 F (39.4 C) and 106 F who had the clinical picture of heatstroke, classifying their condition as "border line hyperpyrexia." It would seem that a transition could exist between border line hyperpyrexia and heatstroke, whereby the body temperature might not exceed the arbitrary value of 106 F. In the heat victim, fever is a manifestation of the body's inability to dissipate heat. All agree that the absence of sweating is the primary defect, the mechanism of which is not well understood. The duration of time between defective sweating and the appearance of an elevated body temperature might lag behind other clinical manifestations of heatstroke. In terms of potential morbidity and mortality, particularly in an aged group, patients with body temperatures below 106 F and the other signs of heatstroke still represent an acute medical emergency. We have, therefore, included as heatstroke victims acutely ill patients with hot, dry skin and central nervous system signs, even though some of them have not exhibited an absolute body temperature in excess of 106 F. Of the 100 cases, there were 39 that fell into this group. The other signs of the heatstroke syndrome were present, and four of these patients eventually died. In none of these patients were there the clinical findings associated with heat exhaustion.

Present Study

An analysis of all admissions for heatstroke to the medical wards of the St. Louis City Hospital in a three-year period, 1952-1954, was made. These patients had been seen in the receiving room first, where eligibility for admission was determined on the basis of the clinical picture. On many occasions definitive treatment to lower the body temperature had already been instituted before transfer to a medical ward. Complete histories were taken and physical examinations and routine blood and urine examinations were done as soon after arrival in the ward as possible. In selected cases other studies were made: determinations of levels of sodium, chloride, potassium, blood urea nitrogen; studies of carbon dioxide–combining power; spinal fluid examinations; and liver function studies.

Of the 100 patients, 59 were males and 41 females. This is in contrast to previous studies, in which the preponderance of males was noted. All were white. The ages of these patients varied from 26 to 88 years, with a predominate number over 60 years old. Table 1 shows the distribution by age and the subsequent number of deaths. There was a large incidence of associated diseases, particularly of the degenerative type, in the older patients. Table 2 lists the associated diseases encountered. It is noted that 84% of the patients had some involvement of the cardiovascular system as determined clinically. The over-all incidence of alcoholism could not be determined, although 23 of the 74 patients (30%) able to give histories admitted a record of alcoholic intake prior to the onset of their heatstroke. There were five deaths in this group.

In 74 patients for whom a clinical history could be obtained, the prodromal symptoms included nausea, vomiting, vertigo, headache, muscle cramps, a feeling of hotness, and dyspnea, which were similar to those

TABLE 1.—*Incidence of Heatstroke by Age of Patient*

Age Group	No. of Patients	No. of Deaths
21-30	2	0
31-40	3	2
41-50	7	1
51-60	18	2
61-70	30	4
71-80	30	5
81-90	10	3
Total	100	17

of previous reports. Seventy-five per cent had noted decreased sweating prior to their admission to the hospital. Observations of Ferris and others [2] were similar. Twelve per cent noted polyuria. There were three patients who gave a history of previous heat injury. Only seven patients stated that their symptoms began suddenly. Twenty-eight had symptoms for less than 24 hours; there was only one death in the group. The greatest number of patients had symptoms for two to five days. The relatively long duration of the prodromal symptoms in the majority of patients probably represents transitional symptoms of fluid and electrolyte imbalance heralding the onset of the hyperpyrexia, the absence of sweating, and central nervous system signs of heatstroke.

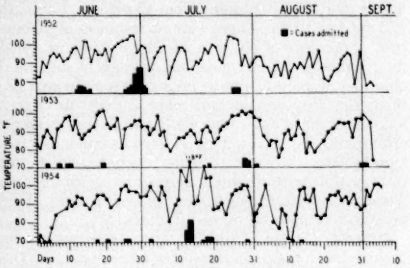
Climatic Temperature.—The year of 1952 was the first year of prolonged heat since the heat waves of 1934 to 1936, having 68 days with an average temperature of over 90 F. In 1953 and 1954 there were 79 and 72 days with temperatures over 90 F respectively. The figure represents the daily mean temperature for St. Louis as obtained from the U. S. Weather Bureau and

TABLE 2.—*Incidence of Other Conditions in Total Heatstroke Patients and Deaths*

Condition	Incidence in Total Patients, %	Deaths Within Group, %
Arteriosclerosis, general	40	12
Cardiovascular arteriosclerosis	35	9
Cerebroarteriosclerosis	9	1
Alcoholism	30	16
Diabetes	7	2
Renal disease	4	0
Chronic pulmonary disease	4	0
Liver disease	3	2
Blood dyscrasia	2	0
Malnutrition	2	2
Duodenal ulcer	1	0

the number of admissions for heatstroke to the St. Louis City Hospital during this three-year period. The average relative humidity ranged from 50 to 60%, with wind movement generally from the south to southeast at about 8 to 10 miles per hour. It is seen that the admission rate follows an early seasonal atmospheric temperature elevation or a prolonged continued one. By far the greatest number of admissions for heatstroke was in the month of June; the next greatest was in July, 1954, when extremely high temperatures were

recorded. Sporadic cases occurred throughout as a result of sustained temperature elevations, usually of three or more days' duration. This relationship between duration of high atmospheric temperature and the incidence of heatstroke has been noted previously.[2]



Relationship of environmental temperatures to admission rates for clinical heatstroke.

Hyperpyrexia.—The presence of fever was noted in all patients in this series. Table 3 shows temperature recorded on admission and the subsequent mortality. It appears that the mortality rate is slightly influenced by the degree of fever upon admission. In the past there has been confusion over the degree of fever. Some have maintained a rigid view, with an absolute body temperature of over 106 F as the main criterion for heatstroke. Ladell [1] designated those patients with temperature below 106 F as having borderline hyperpyrexia; others have included patients with body temperatures below 106 F in their series.[3] In the present series, 44 patients had on admission body temperatures below 106 F. Five of these subsequently developed temperatures recorded over 106 F. Thirty-nine patients were never observed with temperatures over 106 F; of these, four later died. The mortality rate for those patients whose recorded temperatures never exceeded 106 F was 10% as contrasted to 21% for those with

Table 3.—*Temperatures on Admission of Heatstroke Patients and Mortality*

Temperature, F	Total	Deaths
101	1	1
102	8	2
103	8	1
104	13	1
105	14	2
	44	7 (16%)
106	15	1
107	14	4
108	13	2
109	4	1
110	9	2
111	1	0
	56	10 (17%)

temperatures of 106 F or more upon admission or subsequently.

Skin Changes.—The absence of sweating was noted in that all of our patients had a hot, dry skin on admission. There were no cases of purpura and no recorded heat rash. Twenty-seven patients had evidences of a systolic blood pressure below 100 mm. Hg; however, hot, dry skin and a bounding pulse differentiated this symptom from the usual picture of peripheral circulatory collapse. Nine (33%) of these patients died, indicating the poor prognosis accompanying the presence of a systolic pressure below 100 mm. Hg.

Central Nervous System Signs.—Ninety-eight of the 100 patients exhibited some central nervous system abnormalities, varying from lethargy to coma. The greatest risk to life occurred in the comatose group.

Table 4.—*Relation of Temperature and Level of Consciousness*

Temperature, F	Normal	Lethargy	Disorientation	Stupor	Coma	Deaths
101	0	0	0	0	1	1
102	1	0	1	1	4	2
103	1	2	2	1	0	0
104	0	0	4	6	4	2
105	0	2	3	7	0	2
106	0	0	1	4	10	1
107	0	0	3	4	7	4
108	0	0	0	3	11	2
109	0	0	0	0	7	1
110	0	0	0	1	9	2
111	0	0	0	0	1	0

Of the 100 patients, the level of consciousness upon admission was normal in 2; 4 were lethargic; 14 were disoriented (1 death); 27 were in a state of mania or stupor (4 deaths); and 53 were in coma (12 deaths, a mortality rate of 25%). It was observed that the higher the temperature (table 4), the more severe the central nervous system signs, although exceptions were noted. Three patients who had temperatures of 107 F (41.3 C) on admission were only disoriented. Nine patients whose body temperatures were less than 105 F (40.5 C) were observed in coma, again emphasizing the variability of the degree of hyperpyrexia.

Laboratory Observations.—A variety of clinical laboratory procedures was available for analysis. Routine blood counts and urinalyses were available on almost all patients (table 5). As expected, these proved of little value in estimating prognosis. Halden [4] has recently reviewed the hematological findings in heatstroke. The question of the effects of dehydration in heatstroke cannot be answered from our data, inasmuch as determinations of blood volumes were not

Table 5.—*Laboratory Data* in Patients with Heatstroke*

	Total Cases, %
White blood cell count (89) above 11,000	55
Red blood cell count (56) below 4,500,000	55
above 5,500,000	9
Hemoglobin level (61) below 12 gm./100 cc.	9
above 15 gm./100 cc	7
Urinary specific gravity (74) below 1,020	72
Albuminuria (78) 1+	60
Significant pyuria (68)	20
Blood urea nitrogen (61) above 20 mg /100 cc	42
Liver Function Tests	
Total protein (15) above 7.5 gm.	13
Albumin (15) above 3.0 gm.	100
Globulin (15) above 2.5 gm.	100
van den Berg (15) above 1.0 mg./100 cc. total	33
Sulfobromophthalein (4) over 20% retention	100
Alkaline phosphatase (11) below 4 King-Armstrong units	100
Prothrombin time (11) below 50%	100

* Figures in parantheses indicate total number of determinations on each test.

done. The available data in terms of the routine laboratory tests indicating dehydration—determinations of hemoconcentration and increased total proteins—were not borne out in those patients for whom results of these tests were available. Only five patients (9%) showed a total erythrocyte count above 5,500,000; four

of these had temperatures in excess of 106 F. Six patients (13%) had hemoglobin levels above 15 gm. per 100 cc.; three of these had temperatures over 106 F, and two of them had temperatures between 102 F (38.8 C) and 104 F (40 C). Only two patients (13%) of those in whom values of total serum proteins were determined showed increased values over 7.5 gm. One had a temperature of 106.4 F and the other 104 F.

Blood urea nitrogen determinations were available on 61 patients (table 5). Twenty-nine patients exhibited an elevation of over 20 mg. per 100 cc. Nine deaths occurred in this group, indicating the seriousness of this chemical finding. Miscellaneous liver function tests were done on some patients but on too few for comparison (table 5).

Electrolytes.—Serum sodium, potassium, chloride, and carbon dioxide–combining power determinations were available on roughly one-half of the patients

TABLE 6.—*Electrolyte Determinations*

	Total No.	Deaths of Patients, No.
Sodium		
43 determinations; normal, 135-145 mEq./l.; range, 124-171 mEq./l.		
Normal	25	4
Below 135 mEq./l	7	2
Above 145 mEq./l	11	3
Chlorides		
47 determinations; normal, 96-105 mEq./l.; range, 90-138 mEq./l.		
Normal	22	4
Below 96 mEq./l	5	1
Above 105 mEq./l	20	3
Potassium		
44 determinations; normal, 4.0-5.0 mEq./l.; range, 2.7-6.4 mEq./l.		
Normal	13	1
Below 4.0 mEq./l	27	4
Below 4.0 mEq./l	12	
Below 3.5 mEq./l	15	
Above 5.0 mEq./l	4	4
Carbon Dioxide—Combining Power		
38 determinations; normal, 21-30 mEq./l.; range, 11-34 mEq./l.		
Normal	28	5
Below 21 mEq./l	14	3
Above 30 mEq./l	1	0

(table 6). In general, serum sodium concentrations were normal, potassium levels tended to be decreased, values for chlorides were normal or slightly elevated, and carbon dioxide–combining power was within the normal range. It is of interest that salt depletion was not conspicuous in our series, and the degree of hyponatremia and hypochloremia observed was of a mild nature, never approaching the extremely low values reported by Talbot in heat cramps.

Levels of sodium and chlorides were elevated in about 20% of those patients tested. It is interesting that the vast majority of these patients—10 patients out of 11 with serum sodium level elevations and 12 patients out of 20 with elevated levels of chlorides—fell in that group of patients whose temperatures did not exceed 106 F. Most of these patients with increased levels of serum sodium and chlorides also had azotemia and lowered carbon dioxide–combining power, indicating dehydration or prerenal azotemia. Hyperkalemia occurred in four patients, all of whom died.

Special Laboratory Examinations.—The cerebrospinal fluid was examined in 29 patients. In all, it was described grossly as being crystal clear. Of 16 patients in whom cerebrospinal fluid pressures were taken, 15 had pressures below 300 mm. of spinal fluid. One patient had a recorded spinal fluid pressure of 360 mm. There were 25 determinations made for spinal fluid protein; in 9 (36%) the protein value was over 40 mg. per 100 cc., ranging from 42 mg. per 100 cc. to 152 mg. per 100 cc. There were no instances of pleocytosis or presence of blood in the 29 specimens of spinal fluids examined. Determinations of levels of sugar and chlorides were too few to be significant. In five patients electroencephalograms were made; those of four were interpreted as normal, while one showed a diffuse arrhythmia that cleared on a later examination two months later. In three patients psychometric studies were made, with findings compatible with organic damage; repeat examinations in one patient three months later showed normal findings.

Hospital Course.—Clinical improvement generally occurred with the reduction of body temperatures. The central nervous system symptoms persisted the longest. The duration of fever was variable: 8 patients had normal temperatures within the first 24 hours; 56 patients were afebrile by the fourth day; and 13 patients showed a labile temperature course for 7 to 14 days. There were 17 deaths. Seven deaths occurred in the first 24 hours, and an additional seven patients died in the first six days. One patient died within one hour of admission; three each within 12 and 24 hours; one on the 2nd day; three on the 3rd day; one each on the 4th, 5th and 6th days; two on the 9th day; and one on the 13th day. The longest duration from admission to time of death was 13 days. The cause of death was acute left ventricular failure in eight patients and uremia with "anoxic nephrosis" in two. The remaining seven deaths were attributable directly to the effects of the heat syndrome.

Treatment.—The management of these patients consisted in the rapid application of procedures to reduce the body temperature, provision of adequate tissue oxygenation by the treatment of shock, balance of electrolytes and fluids, prevention of bacterial complications, and consideration for the underlying disease process, inasmuch as most of our patients were of the older age groups. Defervescence was accomplished by total immersion in an ice bath with vigorous massage until rectal temperatures were 102 F. At this point the patient was transferred to a dry bed and closely observed. Nasal administration of oxygen was started immediately, and, in those patients with systolic blood pressures below 100 mm. Hg, arterenol (Levophed) was administered. Fluid therapy was given cautiously, with the total volume never exceeding 3,000 cc. per day. For the most part, 5% dextrose in distilled water or isotonic sodium chloride solution was used. Electrolyte values were determined and corrections made when indicated. In a few patients with shock, cortisone was administered. All comatose patients received penicillin prophylactically.

Comment

The ill-effects of a prolonged high environmental temperature in man are due to the interference in the normal regulatory mechanisms that dissipate body heat.

At an environmental temperature of 86 F (30 C) the amount of body heat that can be lost by convection, conduction, and radiation is drastically reduced. With higher environmental temperatures (over 95 F [35 C]) the only method of heat loss is by evaporation with conversion of sweat to water vapor. Evaporation is influenced by the environmental humidity and movement of air. The higher the relative humidity and the lower the air movement, the less efficient is the sweating mechanism. When the sweating mechanism for heat loss fails, the syndrome of heatstroke results, characterized by fever, the presence of a hot, dry skin, and various central nervous system symptoms and signs. The seriousness of heatstroke is attested to by the high mortality. The published figures vary from 38% to 70%.[5] The mortality rate in our series was 17%. We believe the improved mortality rate to be due to the rapid methods of cooling used, the use of pressor substances to maintain blood pressure, the prophylactic use of antibiotics, and the availability of clinical means of determining levels of serum electrolytes. Some of the latter methods of treatment were not available to previous workers. The use of adrenocortical hormones in heatstroke has been previously suggested [6] but is still to be evaluated in this syndrome. Our brief experience with nine patients given cortisone or hydrocortisone in the usual dosage is not sufficient to comment on. These drugs were used in the "poor-risk" patient, and it would be unfair to evaluate their effects only on this group. Theoretically, the capillary damage and adrenal necrosis seen in heatstroke would suggest benefit with the use of these agents.

Because of the seriousness of the problem of treatment of these individuals, it would seem rational to appeal for effective prophylaxis of the heat syndrome. On the basis of our study, this would be practical if the following points were kept in mind by physicians likely to see patients under hot climatic conditions. Heat victims can be anticipated if unusual late spring or early summer elevations of atmospheric temperature, over 95 F, occur or if extremely high temperatures, over 100 F, occur later in the summer or early fall. The greatest risk of heatstroke is early in the year with the advent of high temperatures that persist for 48 or more hours. This undoubtedly is due to the abruptness of the onset of environmental heat without an opportunity for acclimation to develop.

Patients with cardiovascular disease are particularly vulnerable, as shown by the high rate of heatstroke in this group. Eighty-four per cent of the patients had, by history, physical findings, or laboratory diagnosis, an involvement of this body system. Prompt measures to avoid further heat exposure in this group at the onset of the prodromes should materially reduce the risk of heatstroke. The relatively long prodromes with the multitudinous symptoms—nausea, vomiting, vertigo, headache, muscle cramps, feeling of hotness, and dyspnea—should be a caution sign to the physician when there is unduly hot weather in the community. That effective measures for cooling are available is seen by the reduced number of heat victims admitted at the St. Louis City Hospital for the years 1952-1954 in contrast to the larger number of admissions in the years 1934-1936. The use of air-conditioning units, fans, and other devices will effect a reduction in the number of casualties.

The manifestations of heatstroke are reversible if prompt and effective measures for cooling the body are available, for the heatstroke victim is in some ways analogous to the diabetic who needs insulin. The heat victim is in need of an external means to accelerate heat loss until the temperature regulatory center can regain control. The factors providing reversibility depend upon the history of exposure and the length of time of the prodromal symptoms. Those patients with the shorter duration of symptoms did better.

Prognostically, the following clinical signs pointed to a "poor-risk" patient: the presence of temperature over 106 F, coma, azotemia, hypotension, and hyperkalemia. While not as marked as in previous reports, the presence of temperature over 106 F carried a higher mortality, 21% as compared to 10%. Of the various central nervous system signs, the presence of coma was accompanied by a mortality of 22%. Azotemia occurred in 29 patients, with nine deaths, a mortality of 31%. Hypotension, a systolic blood pressure below 100 mm. Hg, was attended with a 33% mortality. Hyperkalemia occurred in only four patients, two of them also azotemic, but all died. There were 7 deaths (41%) within the first 24 hours and a total of 14 deaths (82%) in the first six days. It would follow that the greatest threat to life is in the first 24 hours but that the next seven days present a constant threat to the patient's life.

Summary

In 100 cases of heatstroke observed during the years 1952-1954 at the St. Louis City Hospital, poor prognostic signs were associated with a temperature over 106 F, coma, uremia, hypotension, and hyperpotassemia. Admissions to hospital for heatstroke follow two different environmental situations: an unusually high temperature early in the spring or late in the fall or a prolonged, continued heat wave. Degenerative diseases play a major role as a precipitating factor in heatstroke. Use of effective means of lowering body temperature and vasopressor drugs for the treatment of shock and the attention given to cases in the "borderline" group have reduced our mortality rate. Prodromal symptoms are present for considerable periods of time, allowing for adequate prophylaxis of this medical catastrophe.

607 N. Grand Blvd. (3) (Dr. Austin).

References

1. Ladell, W. S. S.; Waterlow, J. C., and Hudson, M. F.: Desert Climate: Physiological and Clinical Observations, Lancet **2**: 491-497 (Oct. 14); ibid. **2**: 527-531 (Oct. 21) 1944.

2. Ferris, E. B., Jr.; Blankenhorn, M. A.; Robinson, H. W., and Cullen, G. E.: Heat Stroke: Clinical and Chemical Observations on 44 cases, J. Clin. Invest. **17**: 249-261 (May) 1938.

3. (*a*) Malamud, N.; Haymaker, W., and Custer, R. P.: Heat Stroke: Clinico-Pathologic Study of 125 Fatal Cases, Mil. Surgeon **99**: 397-449 (Nov.) 1946. (*b*) Gauss, H., and Meyer, K. A.: Heat Stroke: Report of 158 Cases from Cook County Hospital, Chicago, Am. J. Med. Sc. **154**: 554-564, 1917. (*c*) Wilcox, W. H.: Nature, Prevention, and Treatment of Heat Hyperpyrexia: Clinical Aspect, Brit. M. J. **1**: 392-397 (March 20) 1920.

4. Halden, E. B.; Jones, F.; Sutherland, D. A., and Muirhead, E. E.: Hematologic Studies in Heat Stroke: Anemia of Heat Stroke with Emphasis on Hemolytic Component, abstracted, Am. J. Med. **19**: 141-142 (July) 1955.

5. Footnotes 2 and 3*b*.

6. Waugh, W. H.: Cortisone and Treatment of Heat Stroke, Ann. Int. Med. **41**: 841-843, 1954.

REMITTENT NECROTIZING ACROCYANOSIS

Edward A. Edwards, M.D., Boston

• *Pain in hands and feet, with areas of coldness and cyanosis, was observed in 20 patients. The group included both sexes, all ages from the fourth to the ninth decade of life, and both smokers and nonsmokers. Attacks were not limited to any one time of the year.*

Material for microscopic study was obtained incident to amputation of toes in two cases and by biopsy in nine additional cases. Characteristic findings were perivascular inflammation, intimal proliferation in the arterioles of the skin, and occlusion of the capillaries of the skin by hyaline thrombi.

Remissions occurred in all cases but only after an unpredictable intensity and duration of symptoms. Amputation of a toe became necessary in each of two cases. Lumbar sympathectomy was done, but with little effect, in one case.

The phrase remittent necrotizing acrocyanosis describes this condition objectively. Rest, sedation, and warmth are beneficial; cessation of smoking and use of vasodilator drugs are helpful. Functional vascular spasm and organic occlusion are both factors in this disease.

This is a study of a group of patients in whom acral ischemia appears to have been caused by some malady quite distinct from the usual vascular disorders. The characteristic symptoms are symmetrical cyanosis, coldness, and pain in the hands or feet, often with necrosis of the tips of the fingers or toes; these appear suddenly in late adult life, in attacks of some months' duration without regard to season, with spontaneous remissions, and often with recurrence. In delineating this malady, care has been exercised to exclude, as well as one can, other entities capable of causing similar effects. These are, particularly, ordinary chronic acrocyanosis, Raynaud's disease, generalized scleroderma, arteriosclerosis, blood dyscrasias, thromboangiitis obliterans (Buerger's disease), and frostbite. There is some evidence that occlusion of small vessels is present, but it is not certain that this is the basic pathology. It therefore appears desirable, for the present, to characterize the disorder by the term remittent necrotizing acrocyanosis, implying its clinical character. Brief mention has been made previously of the present group of cases.[1]

This syndrome has received only sporadic attention in the literature. Raynaud included several instances in his heterogeneous collection.[2] Hutchinson, in 1891[3] and 1896,[4] clearly indicated that symmetrical cyanosis and necrosis could occur apart from the paroxysmal reaction to cold and emotion that Raynaud had defined. In 1934 Lewis and Pickering tabulated from the literature several varieties of symmetrical gangrene of the digits not related to Raynaud's disease proper and added two cases of their own.[5] Their report is noteworthy for the emphasis on organic occlusion of small arteries as the responsible pathology.

Material

Twenty patients were studied over a period varying from 2 to 17 years. Three patients died from coronary heart disease two, three and one-half, and five years, respectively, after their initial attack. The majority of the patients were in their sixth, seventh, and eighth decades at the time of their first attack; five patients were in the fourth, fifth, and ninth decades. There were 13 men and 7 women, yet the disease is probably evenly distributed between the sexes, since the men included a group of seven patients from the Massachusetts Soldiers' Hospital. Thirteen patients were smokers; the remainder were not.

Pathology

Biopsies were performed in nine patients; these were of the skin and subcutaneous tissue of fingers or toes in eight, of the forearm and leg in one. In each of two patients a toe was amputated and was available for study. A frequent finding was partial or complete obstruction, by intimal proliferation, of arterioles and small arteries in the dermis or subcutaneous tissue. Perivascular inflammation, usually of a lymphocytic nature, was also noted. Hyaline thrombi were commonly seen occluding dermal capillaries. Smaller parietal hyaline masses were less frequently observed in some arterioles and small arteries.

Clinical Picture

An attack occurred at any time of the year, about half of the attacks starting in the warm months. In one patient each of his two attacks followed closely on an abdominal operation. In another patient pneumococcic pneumonia preceded the attack. In none of the other patients were there any noteworthy precipitating events. There were no prodromal and no constitutional symptoms. The fingers or toes, or both, were noted to become gradually cold, cyanotic, and painful, reaching a peak of severity in days or weeks. The changes in the upper extremities were usually limited to the fingers, but in the lower extremities the cyanosis often spread to the entire sole and heel, as well as to some spots on the dorsum of the foot (fig. 1). All extremities were involved in 11 patients, invariably more severely in one pair than in the other. In nine patients the fingers alone were significantly involved. The symptoms were unaffected by the ambient temperature, except when difficulty was present during the winter and when exposure to the outside air increased the severity. Pain was a quite constant feature of finger involvement; it was inconstant in the feet and toes. Pain was much increased when necrosis developed in the form of fissures or small ulcers at the fingertips or, rarely, as chronic paronychia.

Associate in Surgery, Peter Bent Brigham Hospital, and Associate Clinical Professor of Anatomy, Harvard Medical School.

Read before the Ninth Clinical Meeting of the American Medical Association, Boston, Nov. 30, 1955.

The coldness and cyanosis were also the prominent findings on examination. The cyanosis was often intense, but frequently changeable from one moment to the next. These changes were incompletely removed by vasodilating agents or maneuvers. The pulses at the wrists and ankles were normal by digital or oscillometric examination. Exceptions comprised a 75-year-old man in whom pedal pulses were absent on one side, a 60-year-old woman in whom a dorsalis pedis pulse disappeared during observation, and a young man in whom the posterior tibial pulse disappeared for one month. The skin showed no obliteration of its creases or other signs of sclerosis. It did sometimes

Fig. 1.—Distribution of painful cyanosis in patient of case 1.

appear thin after attacks of long duration. Pterygium of the nails, which I accept as a sign of severe cold sensitivity or of generalized scleroderma,[6] was only occasionally seen. Sweating was only slightly increased.

Laboratory examination was unrewarding. X-rays of the affected parts were normal. Except for signs of microcytic anemia in one patient and an eosinophilia of 7 to 11% in another, the blood cell counts and smears were normal. Tests for cold agglutinins and globulins were negative. The albumin-globulin ratio was normal, but the globulin value rose in three patients during observation until it was almost equal to that of the albumin.

Treatment has consisted mainly of attempts at vasodilatation by cessation of smoking, the wearing of warm clothes, and the use of vasodilator drugs, including tolazoline (Priscoline) hydrochloride, nicotinic acid, Roniacol (β-pyridylcarbinol) tartrate, and, latterly, Dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine) hydrochloride, as well as sympathectomy. These measures have been variously helpful but have never given complete relief. Lumbar sympathectomy was used in two patients, but each case progressed to amputation of the great toe. Lumbar plus dorsal sympathectomies in a third patient resulted in fairly rapid resolution of difficulty. Dorsal sympathectomy in a fourth patient gave rise to healing of fingertip necroses, but only after some months. With this record of equivocal results and the probability of ultimate remission, vasodilator drugs, especially Dibenzyline, have appeared to be usually preferable to sympathectomy. One patient experienced an attack while receiving cortisone therapy for rheumatoid arthritis (fig. 3); cortisone was used in one patient without relief, but it is being currently employed in another with some improvement.

It is of interest to note the number of attacks and their duration. Six patients have suffered a single attack, lasting one month to one year with recovery, and with no further attacks during observation up to eight years. One patient had one attack lasting 4 years, in which there was necrosis of fingertips, and, finally, after spontaneous healing, has had no further trouble for the past 12 years. Finally, in three patients, symptoms have now been present in one continuous attack lasting two, three, and five years respectively. Sequelae of the attacks have included the acquisition of ready vasospasm on exposure to cold and sensitivity of the fingers on touching rough surfaces or performing heavy manual work. Age and sex differences appear not to have influenced either the pattern of the disease or its severity.

Report of Cases

Case 1 (Massachusetts Soldiers' Hospital).—The toes of a 39-year-old man became blue and painful in July, 1951. There was no history of phlebitis. He smoked 20 to 30 cigarettes a day. Examination in September showed blue, tender toes and cold feet. All the major pulses were present. The patient stopped smoking on request. Three weeks later he was miserable because of tenderness of toes. The left posterior tibial pulse disappeared but reappeared in October, when he was obtaining some relief from Dibenzyline therapy. In November, both feet were again

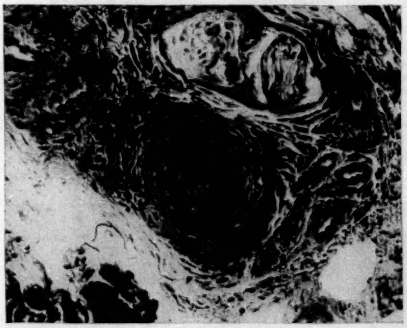


Fig. 2.—Obliteration of the lumen of a subcutaneous artery by intimal proliferation in a biopsy specimen of the left fourth toe of the patient in case 1. Verhoeff's elastic tissue stain, × 200.

badly discolored (fig. 1), with much tenderness on the lateral edge of the left foot and heel. In February, 1952, the process was still active. Biopsy of the left fourth toe was done. It showed moderate perivascular lymphocytic infiltration, rare capillary agglutinative thrombi, and occlusion by intimal proliferation of an artery in the subcutaneous tissue (fig. 2). As spring advanced, he began to feel better. He has had no further trouble for the following three and one-half years.

Case 2 (New England Center Hospital).—A 57-year-old man, on about the first of May, 1948, and without any premonitory difficulty, noted gradually increasing coldness of the fingertips of both hands, followed in a few days by dark spots beneath the nails and on the tips of several fingers. In a few days this progressed to ulceration and pain became prominent. The remainder of the history was not remarkable, except for angina

pectoris. Examination one month after onset showed cyanosis and coldness of the fingers, with absorption of the fingertip pads and superficial ulceration (fig. 4). All major pulses were excellent. There were no cervical ribs, and tests for scalenus compression were negative. General examination and laboratory tests

Fig. 3.—Digital necrosis and cyanosis in a 62-year-old man with rheumatoid arthritis who received cortisone therapy. Single attack of one month's duration. (Reproduced with permission from Friend and Edwards: *A. M. A. Arch. Int. Med.* **93**: 928 [June] 1954.)

were not remarkable. Cessation of smoking and treatment with nicotinic acid were followed by immediate improvement, with complete relief at the end of the third month of the attack. The patient has remained well for the ensuing seven years. His doctor

Fig. 4.—Ulceration of fingertips in patient of case 2. The location of the ulceration at the tip of the left midfinger is typical. The ulceration of the two index fingers is in an atypical location.

writes: "Occasionally he has had very minor numbness and coldness of these fingers in cold weather. The fingers are also still hypersensitive to rough surfaces."

Case 3 (Massachusetts Soldiers' Hospital).—In August, 1951, during his convalescence from splenectomy for arteriosclerotic aneurysm of the splenic artery, a 63-year-old man developed coldness, cyanosis, and tingling of the toes. He gave a history of a similar attack three years earlier, following a nephrectomy for calculus. That attack had terminated spontaneously after three months. Examination showed coldness and cyanosis of all the toes. Excellent pulses were present. Heparin sodium and Roniacol were given. By October, the left foot appeared normal, but necrosis of the tips of the first three toes of the right foot was present. In November, the necroses healed after small eschars had been shed. Cyanosis continued until February, 1952. Biopsy study of a toe then showed slight acute inflammation about dermal capillaries. The patient has been well for the ensuing three and one-half years.

Case 4 (Massachusetts Soldiers' Hospital).—A 54-year-old man suffered a minor contusion of the right great toe in September, 1948. He stopped smoking by advice. Because of continued pain in the toe, a right lumbar sympathectomy was performed elsewhere in April, 1949. Pain nevertheless continued and spread to the other toes. When first seen, in November, 1949, a painful fissure had developed at the tip of the great toe. The foot showed excellent sympathectomy effect, except that the first and second toes were cold and showed blue mottling. The left foot was cold, sweaty, and cyanotic. Both posterior tibial pulses were of good quality. The remainder of the examination and the laboratory findings were normal. The patient refused a transmetatarsal amputation but allowed removal of the right great toe. The wound healed promptly. Microscopic examination of the toe and of a later toe biopsy specimen showed occasional hyaline thrombi in the capillaries. In February, 1950, he began to experience burning pain in the toes of the left foot. By August, pain and cyanosis were extreme in the left foot, as well as in the right fourth toe, in a few spots of the dorsum of the right foot, and also in the left fifth finger. Reluctantly, we acceded to the patient's request to perform a left lumbar sympathectomy; his symptoms continued. In October, the albumin-globulin ratio had changed from 2.1:1 to a new value of 1.1:1. Symptoms appeared and waned through the fall and winter months, with fair remission in the spring of 1951. The process returned in both feet with moderate severity in the following fall and winter but abated in the spring of 1952 and has been inactive since.

Case 5.—A 45-year-old man was first seen in November, 1939, for painful ulceration of the right middle finger. He had had no difficulty with his extremities until the previous fall, when he began to experience numbness and coldness of the fingertips on exposure to cold. In the spring, small areas of necrosis developed on fingers of the right hand and, during the summer, on the left thumb and index finger. In September, the present ulceration developed on the right middle finger. The patient complained of sensitivity of the fingers on exposure to cold and to pressure. Examination showed a 1.5-cm. area of superficial necrosis of the right middle finger, with puckered scars of tips of almost all the other digits. Excellent radial and small ulnar pulses were present. General examination was not remarkable. Treatment consisted mainly of cessation of smoking and protection of the fingers from trauma and cold. Remission occurred only after four years, or a total of five years from the onset of symptoms. No new attacks have occurred in the ensuing 12 years. The patient continues to be sensitive to cold and accidental trauma.

Case 6.—A 61-year-old woman complained, in May, 1953, of painful hands and fingers. Sudden pain and slight swelling of the hands, left forearm, and feet were first noted the preceding December. No antecedent difficulty had been present except for a common cold. Cyanosis of the hands began in April, 1953. The patient had been a moderate smoker but stopped smoking at the onset of the illness. Although she was examined on a warm day, the hands and feet were cold and showed a mottled cyanosis that came and went. All major pulses were normal, and examination was otherwise not remarkable. No pathology was disclosed by the x-ray or by repeated laboratory examinations. No true remission has occurred over the ensuing two and one-half years. To the symptoms described has been added the occasional appearance of a drop of blood at a fingertip. No obvious necrosis has been seen. The right dorsalis pedis pulse disappeared in 1954. Dibenzyline therapy resulted in moderate improvement, although pain has often persisted in the presence of good vasodilatation. She was most comfortable while taking prednisone (Meticorten) in the summer of 1955. It is planned to combine this drug with Dibenzyline therapy this fall, since symptoms are again severe.

Comment

Delineation of Disorder.—There is always the danger, in attempting to delineate a syndrome whose etiology is unknown, that diverse disorders having some symptom in common may be mistakenly grouped as an entity. Several disorders may be separated from the presented syndrome with some confidence. Ordinary acrocyanosis is a chronic, unremitting disorder, in which, as Lewis and Landis showed, arteriolar spasm is responsible.[7] The other conditions mentioned are all seen with greater frequency than remittent necrotizing acrocyanosis and will usually be ruled out rather easily if they are thought of. A previous publication summarized their major diagnostic characteristics.[8] Occasionally, the diagnosis may depend on long-term observation, particularly in the cases of scleroderma and arteriosclerosis. Frostbite poses an unresolved problem. Patients who have suffered frostbite occasionally show a symptom complex much like that presented, but the rarity of its occurrence among large groups of frostbitten patients suggests the possibility that the frostbite may have been an incident in the course of some other vascular disease.

There are some varieties of acrocyanosis with necrosis whose features differ somewhat from the presented disorder. In some cases hypesthesia is prominent. Several examples, probably representing various neurological disorders, were collected by Barlow[9] and by Cassirer[10] under the heading of "akroasphyxia chronica." An endarteritis of small vessels has occasionally been demonstrated, as in such a patient presently under our care but not included in the presented group.

It is uncertain whether there is an identity between the presented syndrome and symmetrical cyanosis and gangrene occurring in acute infections, such as seen by Lewis and Pickering. Three of their cases complicated typhus. I have had the opportunity of studying several cases of peripheral cyanosis and gangrene in typhus in Morocco and have seen the pathological material. The clinical and histological pictures are distinctive and differ from those of this disorder.[11]

Further variants of peripheral cyanosis and gangrene are found in individual case reports. In one of Hutchinson's cases there were patches of gangrene on the knees and hips as well as the acral parts of the limbs.[4] In a case report from the Massachusetts General Hospital[12] cyanosis of the hands and feet with gangrene of the finger tips was associated with hypertension. At autopsy an endarteritis was found in the fingers and the changes of malignant vascular nephritis in the kidneys. At our hospital, cyanosis of the toes developed rapidly in a patient dying from carcinoma of the liver. Pathological findings in the feet were identical with those seen in the biopsy specimens of the reported group.

Significance of Pathology.—Even a conjecture of etiology cannot rest on the meager pathological studies reported. Autopsy material is badly needed. It would be of particular interest to know the condition of the arteries in the palms and soles, especially since Lewis and Pickering found endothelial proliferation and recurrent thrombosis in the arteries of the hands and fingers in two cases, probably fitting the category of remittent necrotizing acrocyanosis.

In a former publication,[8] it was emphasized that hyaline thrombi in small vessels, such as were found in the present material and as mentioned in the literature, are the result of slowing of the blood stream from any cause and cannot be looked upon as a specific finding. One deduction can safely be made from our data: organic obstruction of small arteries and arterioles accompanies the vasospasm of the involved parts. To Raynaud, symmetry of gangrene indicated causation by vasospasm. The findings here presented lead to agreement with the thesis of Lewis and Pickering that "this cannot now be allowed, for symmetry is known in cases of gangrene clearly arising out of arterial disease. . . . There is increasing evidence in the group of cases as a whole, that when gangrene occurs, a structural change such as thrombosis has happened and permanently plugs the vessel."

Treatment.—Specific treatment must await more knowledge of the pathogenesis. It appears logical to advise rest of the parts, sedation, and medical measures to promote vasodilatation. The latter include a warm atmosphere and warm clothing (except for cases at their peak of severity during hot weather), cessation of smoking, and the use of vasodilator drugs. Dibenzyline has been the most useful medicament, but new drugs in this category are appearing from time to time and may be tried.

The irregular and usually disappointing results of sympathectomy are probably due to the organic occlusion of the acral vessels—a situation resembling that seen in scleroderma. Moreover, one hesitates to advise the operation when symptoms may soon remit. As in scleroderma, the severity and duration of symptoms may influence the decision to operate.

Summary

Twenty patients showed symmetrical coldness, cyanosis, and pain of the hands or feet—often with necrosis of the tips of the fingers or toes—that appeared suddenly in late adult life, in attacks of some months' duration without regard to season, with spontaneous remissions, and often with recurrence. Amputation was necessary in two patients, each of whom lost a toe. The term remittent necrotizing acrocyanosis is applied to the disorder. The etiology is not known. Biopsy has shown perivascular inflammation and endothelial proliferation of small arteries and arterioles of the skin. Hyaline thrombi seen in fine vessels are considered a nonspecific effect of sluggish blood flow. One may deduce that organic obstruction accompanies the evident vasospasm. Treatment has consisted of rest, sedation, and vasodilating measures. Sympathectomy has been of relatively little value.

330 Dartmouth St.

This study was aided by a grant from the Massachusetts Heart Association.

Drs. Olga Leary Jr. and A. James McAdams made the pathological studies.

References

1. Edwards, E. A.; McAdams, A. J., and Leary, O. J.: Remittent Necrotizing Acrocyanosis, Proceedings of the American Heart Association, New York, American Heart Association, 1953, p. 61.

2. Raynaud, M.: Local Asphyxia and Symmetrical Gangrene of the Extremities, in Selected Monographs, London, England, New Sydenham Society, 1888.

3. Hutchinson, J.: Severe Symmetrical Gangrene of the Extremities, Brit. M. J. **2**: 8, 1891.

4. Hutchinson, J.: Symmetrical Acro-Sphacelus Without Raynaud's Phenomena, Arch. Surg. (London) **7**: 201, 1896.

5. Lewis, T., and Pickering, G. W.: Observations upon Maladies in Which the Blood Supply to Digits Ceases Intermittently or Permanently, and upon Bilateral Gangrene of Digits: Observations Relevant to So-Called "Raynaud's Disease," Clin. Sc. **1**: 327, 1934.

6. Edwards, E. A.: Nail Changes in Functional and Organic Arterial Disease, New England J. Med. **239**: 362, 1948.

7. Lewis, T., and Landis, E. M.: Observations upon Vascular Mechanism in Acrocyanosis, Heart **15**: 229, 1930.

8. Edwards, E. A.: Varieties of Digital Ischemia and Their Management, New England J. Med. **250**: 709, 1954.

9. Barlow, R.: Appendix to Raynaud.[2]

10. Cassirer, R.: Die vasomotorisch-trophischen Neurosen, ed. 2, Berlin, Germany, S. Karger, 1912.

11. Laure, G.: Remarques cliniques et thérapeutiques sur les gangrènes du typhus, Bull. Inst. d'hyg. Maroc **3**: 59, 1944. Wolbach, S. B.; Todd, J. L., and Palfrey, F. W.: The Etiology and Pathology of Typhus: Main Report of the Typhus Research Commission of the League of Red Cross Societies to Poland, Cambridge, Mass., Harvard University Press, 1922. Pathology of Epidemic Typhus, report of the Committee on Pathology, Division of Medical Sciences, National Research Council, part 1, A. M. A. Arch. Path. **56**: 397 (Oct.) 1953; part 2, ibid. **56**: 512 (Nov.) 1953.

12. Cabot Case Records: Case 19352: Symmetrical Painful Lesions of the Extremities with High Blood Pressure and Gangrene of the Finger Tips, New England J. Med. **209**: 459, 1933.

ANALGESIA WITH NITROUS OXIDE–OXYGEN–CURARE FOR MAJOR SURGERY IN THE POOR-RISK PATIENT

Morris L. Heller, M.D., T. Richard Watson Jr., M.D.
and
Robert C. Storrs, M.D., Hanover, N. H.

• *Experience with more than 200 patients, most of them between the ages of 70 and 95, showed that anesthesia with nitrous oxide, oxygen, and a relaxant of the curare group gave excellent results in major surgery, provided certain precautions were observed. Premedication consisted of secobarbital sodium, scopolamine hydrobromide, and either morphine or meperidine hydrochloride. The type of gas machine is important because of the superiority of the demand-flow, fractional, or nonrebreathing technique. The induction must allow a period of 15 to 30 minutes for denitrogenation, during which the patient settles down to an equilibrium that can be maintained, in some patients, with an oxygen percentage of 30 to 50%. The relaxants used were gallamine triethiodide, succinylcholine chloride, or tubocurarine, the last named being avoided in patients with pulmonary fibrosis, emphysema, or bronchial asthma. The relaxant was administered only when denitrogenation was believed to be complete.*

The anesthesia was kept light, so that the electroencephalograms resembled the records from the wakeful state. Several experiences here described convinced the authors that deep anesthesia greatly increases the danger of hypotension and that changing from ether to nitrous oxide obviated the need for vasoconstrictor drugs. The fact that nitrous oxide does not depress the respiratory center, does not irritate the respiratory epithelium, and does give adequate alveolar ventilation was shown by detailed biochemical studies in 13 patients. It is believed that this type of anesthesia permitted more deliberate, extensive, and definitive operations in poor-risk patients.

As the number of older people in our population steadily increases, the surgeon is faced more frequently with the debilitated, fragile patient in need of surgery. We have found conventional methods of general anesthesia administered in the usual surgical planes are often poorly tolerated by this group. This report summarizes a 10-year clinical study being carried on in the operating rooms and laboratories of the Hitchcock Hospital indicating the safety and value of light analgesia induced with nitrous oxide–oxygen–curare anesthetic as the method of choice in the conduct of major surgery on poor-risk patients. By "poor-risk patient" we mean one who, by virtue of old age, general debility, or specific disease, constitutes a particularly serious problem in the selection and administration of a general anesthetic.[1] In this study we use the term "curare" in the broad sense to include three muscle relaxants, namely tubocurarine, gallamine triethiodide (Flaxedil), and succinylcholine chloride.

It has been shown that depression of the myocardium[2] and vasomotor center may occur in the deeper planes of anesthesia. The integrity of the peripheral vascular bed is impaired as the anesthesia is deepened, with resulting fall in blood pressure and occasionally the production of shock.[3] The respiratory center is also depressed, and adrenal function may be affected adversely as greater depths are reached. The healthy subject can usually adjust to these changes in body physiology, but the poor-risk patient has no such margin. In spite of these observations many authors actually have stressed the concept of safety to be obtained by utilizing the deeper anesthetic levels.[4] They have suggested that light-plane anesthesia may be harmful to cardiovascular function by virtue of nonsuppression of traumatic autonomic reflexes common to surgery and anesthesia.

From Dartmouth Medical School and the Hitchcock Clinic (Drs. Heller, Watson, and Storrs) and the Hitchcock Foundation (Dr. Watson).

Read at the Ninth Clinical Meeting of the American Medical Association, Boston, Nov. 29, 1955.

Because of these differences of opinion, many problems peculiar to light-plane anesthesia demanded further clarification. It is important to know: (1) the level

of anesthesia resulting when nitrous oxide–oxygen is combined with the muscle-relaxant agents for major surgery, (2) the effect of extremely light anesthesia on cardiovascular homeostasis, (3) the effects on cardiac rate, rhythm, and conduction, (4) the respiratory problems, including breath holding, irregular breathing, pulmonary ventilation, bronchospasm, and laryngeal irritability, and (5) the incidence of excitement, movement, swallowing, and vomiting during light anesthesia. This presentation is concerned with solving some of these problems.

Administration of Nitrous Oxide–Oxygen–Curare

Our method of administration of nitrous oxide muscle-relaxant anesthetics has been outlined previously.[1] However, a few important points should be emphasized. The main agent is nitrous oxide. Too much dependence should not be placed on the muscle relaxants. There must be a proper balance between the drugs for premedication, the nitrous oxide, and the "curare" agents. No cyclopropane or ether is used, and local infiltration of the skin incision is not necessary. We do not use thiopental (Pentothal) sodium in the light nitrous oxide anesthetic technique for the poor-risk patient. This agent may at times help the induction of anesthesia, but on the other hand it may complicate the anesthetic effects of nitrous oxide. Thiopental sodium is broken down slowly in the body. When administered too rapidly, it may cause a depression of respiration and also cardiovascular decompensation. In some individuals this drug, even in small amounts, may provoke laryngeal and bronchiolar muscle spasm with their harmful sequelae. We have observed that in patients with chronic pulmonary disease, there are fewer respiratory problems when nitrous oxide is given without the addition of thiopental sodium.

Proper premedication is an important component of light anesthesia with nitrous oxide. This consists of secobarbital sodium, 25 to 100 mg.; morphine, 4 to 8 mg., or meperidine hydrochloride, 25 to 75 mg.; and scopolamine hydrobromide, 0.2 to 0.3 mg. For example, an elderly patient may receive secobarbital, 25 mg., meperidine, 25 mg., and scopolamine, 0.3 mg., one hour prior to induction. Before nitrous oxide is administered, an evaluation is made of the effect of the premedication. We prefer to have the patient sleepy, yet he should answer questions readily. If the premedication is inadequate, we may add secobarbital sodium in 10 to 15 mg. fractional intravenous doses until the proper effect is obtained. Experience is required in estimating the optimal dosage. Overmedication is undesirable because the beneficial effect of light nitrous oxide anesthesia is then neutralized.

Scopolamine is used in preference to atropine because the former has greater sedative properties plus good drying effect. It has been the experience of older anesthetists, who used nitrous oxide extensively before the advent of curare, that this type of anesthesia is handled much more easily when the premedication is with scopolamine.[5] Many authors decry the use of scopolamine in older people and cite the possibility of delirium and mania following administration of this drug. This has not been our experience with a large number of older subjects. We have found that scopolamine is an essential aid in nitrous oxide anesthesia.

Meperidine hydrochloride, 10 to 25 mg., is occasionally also given intravenously in fractional amounts during the early part of the operation. After the first half hour, intravenous supplements rarely are given. Our observations have led us to believe that premedication agents are of most help during the induction until denitrogenation is more complete. Successful administration of nitrous oxide requires a thorough understanding of denitrogenation.[5] Once the patient "settles down" (and this may require 15 to 30 minutes), the administration of the anesthetic becomes easier. The subject remains asleep with administration of less nitrous oxide and more oxygen. Adequate anesthesia with nitrous oxide can subsequently be obtained in some patients with an oxygen percentage of 30 to 50%. We emphasize the fact that induction is the most difficult phase and determines to a large degree the subsequent course of the anesthesia.

We believe that the type of gas machine is important in the administration of nitrous oxide–oxygen anesthesia. The combination demand-flow–circle absorption machine has definite advantages. Clement has pointed out for many years the superiority of the demand-flow, fractional, or nonrebreathing technique for a faster, smoother induction and for rapid complete denitrogenation.[5] Elimination of nitrogen is important in order to provide a higher concentration of both oxygen and nitrous oxide in the alveoli. Furthermore, there is more precise control with the demand-flow machine, whereby the mixture of nitrous oxide and oxygen can be changed from breath to breath, according to the requirements of the patient. During the early period of anesthesia an estimate is made of this requirement and of the individual's susceptibility to nitrous oxide, to curare, and to the analgesic supplements for intravenous use.

Successful light nitrous oxide anesthesia does not depend on the choice of a specific muscle-relaxant drug. We have had good results with any one of three agents: tubocurarine, gallamine triethiodide, and succinylcholine chloride. The muscle relaxant should not be added too early in the induction period. These curare agents should be given only when complete denitrogenation occurs; otherwise there may be a stormy course until the full anesthetic effect of nitrous oxide is realized. Then either tubocurarine or gallamine triethiodide is added in fractional amounts; a succinylcholine chloride intravenous drip also has been used effectively. Use of tubocurarine is avoided in those patients who are prone to develop bronchospasm, namely, those with pulmonary fibrosis, emphysema, or bronchial asthma. For this group, we use either gallamine triethiodide or succinylcholine chloride. At the end of the procedure, muscle tone returns more quickly after use of nitrous oxide than it does after the administration of the more potent anesthetic agents. Prolonged apnea has not been a problem.

When respiratory exchange is diminished, assisted breathing is carried out with the conventional circle

absorption part of the combination machine, and an oropharyngeal or nasopharyngeal airway is routinely inserted. We do not hesitate to intubate if the respirations cannot otherwise be assisted properly. Succinylcholine chloride is used to facilitate intubation prior to pulmonary or cardiac surgery. After time for denitrogenation has elapsed, succinylcholine chloride is administered intravenously up to the point of apnea. While the relaxant is taking effect, the mixture of gases is changed to a 50-50 ratio of nitrous oxide and oxygen and ventilation is vigorously assisted. The larynx and trachea are quickly sprayed with 0.5 to 1% tetracaine (Pontocaine) hydrochloride. The face mask is reapplied and respirations are again assisted with the mixture of 50% oxygen. Then intubation is performed by direct vision and respirations are assisted as necessary. A succinylcholine chloride drip may be continued throughout the procedure, or, more often, after the initial effect of the succinylcholine chloride has worn off, a change is made to intermittent gallamine triethiodide injections. During the surgical procedure the nitrous oxide percentage is varied according to the patient's requirements. At the end of the operation the patient is given 100% oxygen for several minutes in order to supply a high alveolar oxygen concentration during this period when a large volume of nitrous oxide is being released from the body tissues into the lungs.

Major Surgery with Nitrous Oxide—Oxygen Anesthetic

Depth of Anesthesia.—We have made use of the electroencephalogram as a measure of depth of anesthesia.[1] Tracings were taken in the patient before premedication for control purposes; these were repeated after premedication and prior to the administration of nitrous oxide; further tracings were taken at intervals throughout the giving of nitrous oxide and surgery; finally, recordings were made in the postanesthesia period.

Electroencephalographic studies by Courtin, Bickford, and Faulconer with the more potent anesthetic agents have shown that ether, cyclopropane, and thiopental sodium depress the brain wave potential, producing distinct patterns at various depths of anesthesia.[6] Artusio in comparable studies on analgesia with ether reported that "an analysis of electroencephalographic tracings indicated that a distinct pattern could be associated with analgesia, different from that seen in the conscious patient."[7] The pattern when ether was used showed predominantly rhythmic sinusoidal activity of 20 to 22 cps with an amplitude of 30 to 40 μv.

During analgesia with nitrous oxide, on the other hand, our electroencephalographic tracings showed no such changes. In fact, they closely resembled the control record of the wakeful state. There is no alteration in amplitude, rhythmicity, or wave form. A slight slowing of the alpha pattern was noted occasionally, but it always remained within the normal frequency range. A typical electroencephalographic record taken during analgesia with nitrous oxide is shown in figure 1. At this extremely light level of anesthesia, amnesia, unconsciousness, and analgesia are present. When the nitrous oxide concentration is lightened, the patient may show slight movements, shake his head, wrinkle his forehead, or moan. Ordinarily these movements are rarely observed with the technique we have described. Once anesthesia has been induced and stabilized, delirium or excitement is not seen; there is good surgical relaxation from the curare drugs, and swallowing or vomiting does not occur. It should be noted that the electroencephalogram is not necessary in the practical use of nitrous oxide analgesia. As an investigative tool, it has proved helpful.

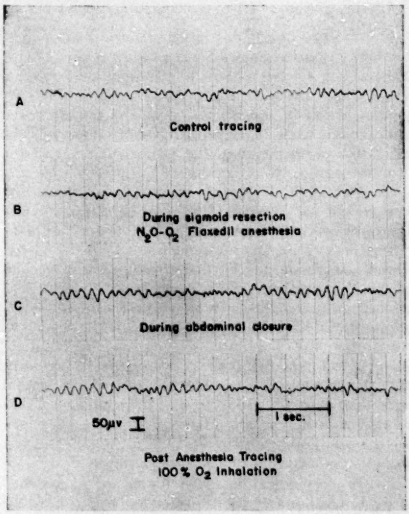


Fig. 1.—Electroencephalographic study of 69-year-old patient during anesthesia with nitrous oxide–oxygen–gallamine triethiodide during resection of sigmoid and oophorectomy for obstructing cancer of sigmoid. *A*, control tracing (prior to premedication) shows slightly irregular 8 to 9 per second alpha waves with some intermittent flattening. *B*, tracing during surgery (duration of nitrous oxide, one hour). No visible effect of premedication is shown or any change from control tracing of wakeful state. *C*, tracing during closure (duration of administration of nitrous oxide, two and one-half hours). Alpha waves more prominent and at times slightly slower (7 to 8 per second), with some periods of intermittent flattening of record. *D*, tracing during use of 100% oxygen with patient awakening; no change in tracing.

Blood Pressure During Anesthesia.—Much can be learned by comparing blood pressure recordings made during anesthesia with ether with those made during the administration of nitrous oxide—oxygen.

It has been observed clinically for a long time that some patients develop a marked fall in blood pressure during or after induction of anesthesia with ether, even in the light-plane surgical stage. Recently Brewster,[2] in an excellent study, elucidated the mechanism of this response. He emphasized the "potential direct depressing effect of ether on the myocardium. In some patients there is insufficient reflex release of epinephrine and norepinephrine from the adrenal medulla and sympathetic nerve endings." Subsequently the cardiac output decreases. Persons with cachexia, persons in

toxic condition, debilitated persons, and those with poor thyroid and adrenal function are especially prone to show a depressed myocardium during administration of ether. These are the very patients who are excellent candidates for light nitrous oxide anesthesia.

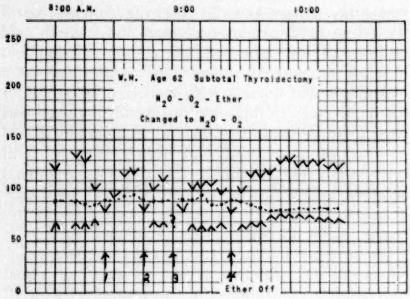


Fig. 2.—Chart showing myocardial depression in 62-year-old patient during anesthesia with ether. First plane, stage 3, occurring at 1, 2, 3, and 4. The use of ether was discontinued and it was "blown off" at these points. With recovery of the blood pressure, ether was again administered, resulting in hypotension on each occasion. At 4 the use of ether was permanently discontinued, and nitrous oxide–oxygen was administered for the remainder of the operation.

We have observed numerous patients with a marked fall in blood pressure during anesthesia with ether. When the level of anesthesia is lightened by "washing out" the ether, the blood pressure tends to return toward the original level. After the elimination of ether, excellent surgical anesthesia can be maintained for long periods of time with nitrous oxide—oxygen plus a muscle relaxant. The blood pressure no longer undergoes the marked depression previously noted.

A 62-year-old patient received nitrous oxide—oxygen—ether anesthetic for a contemplated subtotal thyroidectomy (fig. 2). This patient apparently had become hypothyroid during her medical preparation for thyroid surgery. Whenever a small amount of ether was added to the anesthetic, the blood pressure fell to a low level. By eliminating the ether, the blood pressure returned toward the original level. This occurred four times during the early part of the operation. Finally the use of ether was permanently discontinued, and anesthesia was maintained with nitrous oxide—oxygen. The blood pressure became adequate and maintained a steady course.

Autonomic reflexes may be very disturbing when they occur during anesthesia. Marked vagotonia is frequently noted during anesthesia with ether immediately after the induction. Also reflex vagal stimulation from surgical manipulation of chest wall, rib periosteum, neck, pulmonary hilus, and abdominal and pelvic structures may give rise to hypotension, bradycardia, and auriculoventricular conduction defects. Atropine given intravenously usually offers good protection from excessive vagotonia. Others have used tubocurarine to block vagal impulses. However, the protective effect of curare has not been consistent. Our experience has shown that a lighter level of anesthesia is the more rational therapy for vagotonia occurring during surgery and anesthesia.

A 57-year-old patient (fig. 3) showed a fall in blood pressure and bradycardia after the induction of anesthesia with thiopental sodium—nitrous oxide—ether and intubation. Blood pressure fell from 130/70 to 80/50 mm. Hg, and the patient's pulse rate slowed from 110 to 60 beats per minute. No atropine was used in this case; the ether was blown off and nitrous oxide—oxygen substituted. Tubocararine was later added for muscle relaxation. The blood pressure and pulse rate started to rise after a short interval and within 15 minutes were back to their original level. Vagotonia with hypotension and bradycardia is a rare occurrence during light anesthesia with nitrous oxide.

During anesthesia with ether in upper abdominal surgery, reflex celiac plexus hypotension is often a problem. Treatment of this condition with drugs given intravenously has been disappointing. Some use atropine and others recommend physostigmine salicylate.[4b] We have found that neither drug is very effective in improving this type of blood pressure depression. However, our observations in a large number of patients have demonstrated the beneficial effect of a lighter plane of anesthesia.

An example of this reflex hypotension was demonstrated in a 77-year-old patient (fig. 4) who underwent abdominal surgery. The anesthetic used was thiopental sodium—nitrous oxide—oxygen—ether. During the exploration of the upper abdomen, the blood pressure fell. The manipulations were stopped and there

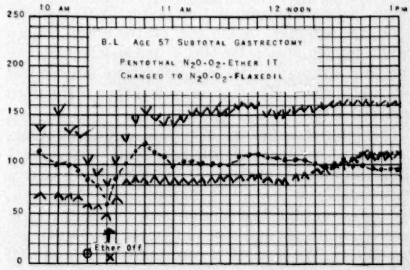


Fig. 3.—Chart of patient aged 57 years showing increased vagotonia following induction of anesthesia with thiopental sodium–nitrous oxide–oxygen–ether. Blood pressure fell to 80/50 mm. Hg and the pulse slowed to 60 beats per minute. At X the use of ether was discontinued and "blown off." Anesthetic was changed to nitrous oxide–oxygen. Gallamine triethiodide was added later. Blood pressure and pulse rate showed a stable course during the light-plane nitrous oxide analgesia. No atropine was used.

was an improvement for a few minutes, at which time further surgical exploration was attempted. The systolic pressure again fell to 75 mm. Hg and the pulse became weak. At this time the administration of ether was discontinued and use of nitrous oxide—oxygen started. There was no further difficulty encountered for the remaining part of the operation (three and one-half hours).

Another example of celiac plexus reflex during anesthesia occurred in a patient aged 58 years who had cirrhosis of the liver with bleeding esophageal varices. Patients with disease of the liver are notoriously poor risks for anesthesia and surgery. Anesthesia was induced with thiopental sodium—nitrous oxide—oxygen—ether and the patient was intubated. Blood pressure prior to induction was 150/80 mm. Hg. During the first two hours of the portacaval anastomosis, there was a stormy course with fall in blood pressure to 85/50 mm. Hg. During manipulation of the upper abdomen, the blood pressure fell to 50 mm. Hg. The pulse became thready at this point. The anesthetic level was lightened by blowing off the ether. Nitrous oxide—oxygen anesthetic plus a succinylcholine chloride drip was used for the remaining four and one-half hours of surgery. Blood pressure was then maintained between 100/50 and 110/50 mm. Hg.

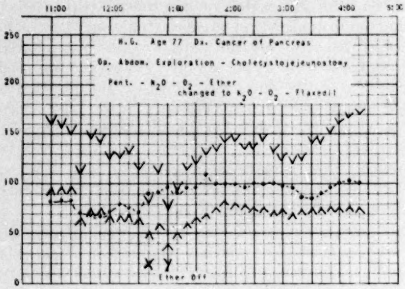


Fig. 4.—Chart of patient aged 77 years showing reflex celiac plexus hypotension during exploration of upper abdomen in carcinoma of pancreas. During anesthesia with thiopental sodium—nitrous oxide—oxygen—ether, blood pressure fell to 80/50 mm. Hg and the radial pulse became weak and thready (X). Manipulations were stopped and blood pressure improved. Further exploration (Y) resulted in another decline in blood pressure to 75/40 mm. Hg. Anesthesia was then lightened by changing to nitrous oxide—oxygen—gallamine triethiodide. There was no recurrence of the hypotension during the remaining three and one-half hours.

Our interest in the use of nitrous oxide was stimulated by experiences of this type with deeper anesthesia. In the case of the poor-risk subject, we believe it preferable to start with nitrous oxide—oxygen in order to avoid the hypotension seen during the early part of anesthesia and also to obviate deleterious reflex effects. We studied a consecutive series of 200 older patients who were anesthetized with nitrous oxide—oxygen muscle-relaxant anesthetic for major surgery. Inclusion of subjects in this group depended primarily on their poor-risk status. The majority were between 70 and 95 years of age. Physical disabilities included diseases of the heart, liver, lungs, and kidneys; many were weak and cachectic. Time under anesthesia ranged from one to 10 hours. Operations included major orthopedic procedures, upper and lower abdominal surgery, radical mastectomy, adrenalectomy, sympathectomy, brain surgery, and pulmonary surgery. Although these patients received many forms of surgical stimuli, a review of the blood pressure charts showed no significant fall in blood pressure in any patient either during the induction or maintenance of anesthesia. In only one instance was a vasoconstrictor drug used. We found the incidence of vagal or celiac plexus reflexes to be insignificant during light anesthesia.

It is interesting to compare the course of anesthesia in another patient aged 58 years (fig. 5) with that of the 58-year-old patient described above. Both had cirrhosis of the liver with portal hypertension and bleeding esophageal varices. The former showed a leukopenia and anemia with increased hemolysis of red blood cells. In this case, the anesthetic given was nitrous oxide—oxygen—gallamine triethiodide. Blood transfusions were withheld during surgery until splenectomy was accomplished. A difficult splenorenal anastomosis was then performed. Although total time of anesthesia was 10 hours, the blood pressure remained stable throughout this prolonged period.

We have noted a marked fall in blood pressure during anesthesia with ether in patients with high spinal cord paralysis. This subject has been studied by McAllister and Root,[8] who have shown pronounced depression of the blood pressure during anesthesia with ether in animals with interruption of function of the spinal cord in the lower cervical region. However, during light anesthesia with nitrous oxide, we have observed excellent cardiovascular homeostasis in similar human subjects who have been operated on for exploration and decompression of the spinal cord.

Elevation of the head and trunk in the anesthetized patient often produces a fall in blood pressure due to interference of the protective carotid and aortic reflexes. With deeper anesthesia, the hypotensive changes are more profound. We have been especially interested in the elderly, hypertensive patient during neurosurgery in the sitting position and have found that with analgesia with nitrous oxide there is adequate compensatory vasoconstriction. The light plane of anesthesia protects the patient against the stress of postural change. A common geriatric surgical problem is fracture of the femoral neck. Light anesthesia has proved to be advantageous for elderly patients with

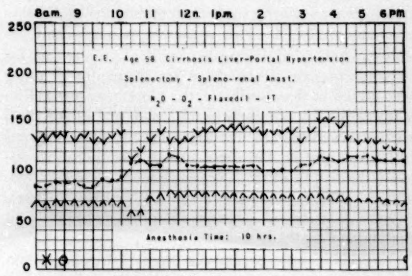


Fig. 5.—Chart of 58-year-old patient with cirrhosis of the liver and esophageal varices with hypersplenism. Patient was a poor risk for anesthesia and surgery. Light nitrous oxide—oxygen—gallamine triethiodide anesthetic was administered from the beginning. Excellent cardiovascular homeostasis was observed during prolonged major surgery (10 hours).

such fractures who may require lengthy surgery and anesthesia for proper bone fixation with the aid of numerous x-rays.

Surgery in a patient with deep shock due to a severe infectious process sets up a serious problem in anesthesia.[9] We have observed that this type of shock responds to neither blood transfusions nor vasopressor drugs. A patient aged 62 years had a large perforation of a duodenal ulcer with massive, diffuse peritonitis of 12 hours' duration. He was in profound peripheral circulatory collapse with a fluctuating fall in blood pressure from 110 to 40 mm. Hg. The pulse rate was 120 to 130 beats per minute. Blood transfusions did not improve his general condition but did raise the blood pressure temporarily. He showed signs of hepatic, adrenal, and renal failure: deep acidotic breathing, confusion, restlessness, and stupor, alternating with mania. There was also oliguria. Prior to induction of anesthesia the blood pressure had risen to 110/70 mm. Hg. An exploration was done during anesthesia with nitrous oxide—oxygen—gallamine triethiodide. Gross soiling of the peritoneum was found with leakage from the duodenal perforation. The duodenum was closed and a gastroenterostomy was performed. His vital signs did not show any untoward change during anesthesia, which lasted two and one-quarter hours. The lowest systolic pressure was 100 mm. Hg and the highest pulse rate was 130 beats per minute. We believe the very light plane of anesthesia maintained throughout the procedure was responsible for the excellent cardiovascular homeostasis in this critically ill patient in profound shock. No vasoconstrictor drug was administered. Electrocardiographic tracings showed no abnormal deviations.

During anesthesia of an extremely light plane there is a rise in blood pressure in a small percentage of patients.[1] The subject who has a labile blood pressure or is actually hypertensive is more likely to show this change. We believe that this is due to sympathoadrenal stimulation. If the myocardium were depressed by nitrous oxide, this rise would not occur. We have not observed any dangerous sequelae from an elevated pressure during levels of light anesthesia. An 88-year-old patient showed a rise in blood pressure during anesthesia with nitrous oxide—oxide—oxygen—gallamine triethiodide for a subtotal gastrectomy because of stomach cancer. Duration of anesthesia was three and one-half hours. For a period of 10 minutes there was an elevation to a blood pressure of 220/110 mm. Hg from 200/100 mm. Hg preoperatively. However, we would prefer to maintain this level rather than experience the precipitous drop that is not unusual during deeper anesthesia in a hypertensive patient of this age group. Hypotension is accompanied by a decrease in flow of coronary blood and predisposes the myocardium of an elderly patient to great danger from coronary insufficiency.

Cardiac Rhythm, Rate, and Conduction.—Our observations of the cardiac mechanism during light nitrous oxide—oxygen anesthesia have already been reported.[1] Since this original series of 53 patients was presented, another 100 patients have been studied electrocardiographically. The results are similar to the original findings. The response of the cardiac mechanism is favorable. Sinus tachycardia and solitary premature beats occur in a small percentage of the patients. Vagotonia, manifested by bradycardia, nodal rhythm, or auriculoventricular block, is a rare occurrence during light anesthesia. Ventricular irritability, manifested by ventricular runs or multiple ventricular foci, is extremely infrequent. The same holds true for T wave and ST segment depression. There is no instance of cardiac arrest. Once anesthesia was induced, the electrocardiograms of some patients were actually improved, with slowing of the cardiac rate, decreased incidence of solitary extrasystoles, and less depression of the ST segment.

Several workers have stressed the increased incidence of cardiac irregularities when endotracheal intubation is performed during light anesthesia. This has not been our experience. In a recent study we took continuous electrocardiograms during the topical spraying and intubation of 25 patients. An increased sinus heart rate was the only change noted. No other arrhythmias were observed.

Respiratory Observations.—An important salutary property of nitrous oxide is that it does not depress the respiratory center. Consequently respirations are full during this type of anesthesia. The patient has the "urge to breathe" and saturation with nitrous oxide and denitrogenation are facilitated. When foreign material is present in the region of the larynx or trachea, the patient may cough or momentarily hold his breath. The airway may be aspirated without provoking severe paroxysmal laryngospasm and bronchospasm, so often seen during administration of thiopental sodium. This difference in the pharmacological action of nitrous oxide and thiopental sodium has tremendous practical significance especially in those patients with bronchial asthma, emphysema, or pulmonary fibrosis.

Patients with pulmonary insufficiency and pulmonary disability constitute one of the most perplexing problems in general anesthesia. Use of spinal anesthetics for major abdominal surgery may be hazardous in this group. Moreover, many individuals who have pulmonary problems require thoracic surgery. The patient with pulmonary insufficiency often shows evidence of bronchospasm and obstruction to the flow of gases. During anesthesia bronchospasm may become more severe or, in some individuals, it may occur for the first time. Thiopental sodium has been implicated in the production of laryngospasm and bronchospasm, probably due to increased vagal activity and the presence of a foreign body, secretions, or instruments. Laryngeal and bronchial spasm are also seen occasionally during anesthesia with cyclopropane.[10] This is often associated with "bucking," forced prolonged expiratory effort, and spasm of the intercostal, diaphragmatic, and abdominal muscles. Atropine has been recommended as an antidote for this condition. Theoretically, atropine should exert a blocking effect at the vagal endings in the smooth

bronchiolar musculature. However, this is often uncertain in man during severe episodes. It is more difficult to explain the beneficial action of atropine at the myoneural junction of the recurrent laryngeal nerve and the striated laryngeal muscles. This drug probably does help by its drying of secretions.[11] On the other hand, succinylcholine chloride is extremely effective in its utter relaxation of laryngeal muscles and the spastic thoracic and abdominal muscles involved in the "bucking" process. However, the effect of succinylcholine chloride on the smooth musculature of the bronchioles is not entirely clear. There may be some unexplained blocking effects of thoracic autonomic ganglions. Recently Peters has shown that "bronchoconstriction produced experimentally in animals by increasing the pCO_2 was not relieved by succinylcholine even when two or three times the dose necessary to cause skeletal muscle relaxation was given."[12]

Ether with nitrous oxide has been used successfully for the asthmatic patient. It has been observed that bronchospasm is relieved when deep anesthesia with ether is produced. However, ether is itself somewhat irritant and the induction period may be stormy with coughing, breath holding, cyanosis, and hypoxia. There may also be a depression of the cardiovascular system. We therefore prefer to use nitrous oxide—oxygen plus gallamine triethiodide or succinylcholine chloride without ether for this type of patient. Nitrous oxide is nonirritating to the respiratory epithelium, and a smooth induction can be expected. We have observed that assisted breathing is readily performed in the patient with pulmonary asthma, pulmonary fibrosis, or emphysema. Adequate exchange of gases can be accomplished. Our impression clinically is that nitrous oxide does not produce bronchospasm, and with nitrous oxide we have not encountered the respiratory problems that are frequently seen with other anesthetic drugs in patients with pulmonary disease.

Because of the observed benign effect of nitrous oxide in patients with pulmonary abnormality, we have also utilized this light method of anesthesia for all types of cardiopulmonary surgery. Usually endotracheal intubation is accomplished with the single lumen tube. In the patient with copious secretions, the double lumen endotracheal bronchial catheter of Carlens is used. This allows individual lung control and frequently greatly facilitates the surgery. Another distinct advantage is the safety with which electrocautery may be used during anesthesia with nitrous oxide—oxygen for thoracic surgery.

Blood Gas Studies During Anesthesia with Nitrous Oxide—Oxygen—Curare

In addition to noting the striking clinical course of these patients, it is important to know the specific blood gas changes that are occurring. During the early part of the anesthesia the oxygen percentage in the demand-flow mixture is 20 to 25%. As the operation proceeds, the oxygen percentage may be increased up to a 50% concentration in the inhaled gases. From preliminary blood gas studies, we have shown that normal oxygen saturation is maintained during anesthesia with nitrous oxide when the oxygen percentage is in the range of 20 to 25.

We have also carried out preliminary studies indicating that adequate, effective alveolar ventilation is maintained during anesthesia with nitrous oxide. Hand-assisted ventilation is used in all cases, whether or not the patients are intubated. Tidal air is maintained at between 500 and 700 cc., with minute ventilation between 8 and 15 liters. Blood samples are drawn from the brachial artery through a Cournand needle with heparin syringes. These have been taken at various stages of the anesthesia and surgery. Determination of carbon dioxide (volumes per cent), oxygen (volumes per cent), and percentage of saturation is done using standard Van Slyke and Neill techniques modified by the method of Goldstein. Determinations of pH are made immediately after the blood is drawn, using a calibrated Cambridge pH meter. Values of pCO_2 have been calculated from the nomogram of Singer and Hastings.

Thirteen cases have been studied in detail. Blood oxygen saturation remained above 90% except during the lung collapse stage in two patients with severe pulmonary abnormality who were undergoing thoracic surgery in whom 82 and 87% were recorded. Mean oxygen saturation in all cases during anesthesia was 96%, with 105% the highest recorded. In three instances the preanesthesia saturation was 87%, rising in the postinduction period to 95, 99, and 94%. In general, pH determinations were in the normal range before induction of anesthesia. There appeared to be a slight gradual drop during anesthesia; characteristic examples are the dropping of determinations from 7.35 to 7.29 and from 7.37 to 7.26 in two patients undergoing pulmonary lobectomy. pCO_2 values were calculated. The mean pCO_2 was 50 mm. Hg with a range between 34 and 63 mm. Hg. In this preliminary study, our observations were made on elderly patients with pulmonary disease. Further studies are now being carried out on more normal subjects. Numerous blood potassium determinations were done in an attempt to note any rise during or at the end of surgery with the patient receiving 100% oxygen. All values were within normal limits.

Comment

Our studies of electroencephalograms in patients during anesthesia with nitrous oxide showed practically no change from the tracings obtained in the wakeful state. It is interesting to note that other anesthetic agents produce distinct patterns at any depth of anesthesia.[6] During the extremely light level of anesthesia obtained with nitrous oxide, there is unconsciousness, analgesia, and amnesia. In our experience, there has been no incidence of memory of any surgical procedure. With the addition of muscle-relaxant drugs, good relaxation in surgery is obtained. If the level should be allowed to become excessively

light, the patient can be quieted more readily at this time than during the original induction of anesthesia. The management of anesthesia becomes relatively easier as the duration of anesthesia increases.

The classic teachings of Guedel are not adequate to describe the light plane of anesthesia with nitrous oxide, in view of the electroencephalographic recordings we have obtained. We need a new classification of anesthetic levels, based on recent observations of major surgery during light-plane anesthesia.[13] For lack of a more precise term, we are referring to this as the level of analgesia. Contrary to traditional ideas, it can be stated that light-plane analgesia is not harmful to cardiovascular function by virtue of nonsuppression of traumatic autonomic reflexes. Actually, depressant vagal and celiac plexus reflexes occur more frequently during the deeper planes, and these untoward changes are obviated by lightening the anesthesia. There is also good evidence that nitrous oxide does not produce myocardial depression of the type that is seen with ether. We have observed a remarkably stable blood pressure during all phases of analgesia with nitrous oxide in the poorest of risks. Furthermore, we believe that endotracheal intubation may be done with safety during the analgesia level. The only change in the cardiac mechanism we have observed is a sinus tachycardia, which is seen occasionally in light anesthesia and does not appear to affect the patient adversely.

Cardiac disturbances during anesthesia have been related to an imbalance of the autonomic nervous system.[4a] Hypoxia and hypercapnia play a role in intensifying this imbalance. The former enhances existing arrhythmias and conditions the myocardium to eventual failure. Recent studies have shown that hypercapnia increases the effects of vagal stimulation on the heart.[14] Carbon dioxide retention has been emphasized as one of the main factors in the production of serious cardiac disturbances, including cardiac arrest.[15] It has not been determined as yet whether the actual level of pCO_2 or the abrupt change in carbon dioxide concentration is the responsible mechanism.[16] Changes in electrolytes, especially the plasma potassium level, are also involved in the altered physiology. In addition, the histotoxic effects on the myocardium from the more potent anesthetic agents must be kept in mind.

In order to explain why cardiac irritability is greater and more frequent during anesthesia than it is in the wakeful state, autonomic imbalance, surgical reflex stimuli, and hypoxia and hypercapnia have all been implicated. We would like to add another important variable, namely, the depth of anesthesia. For we believe that the deeper the anesthesia, the more dangerous are these factors of imbalance, reflex stimuli, lack of oxygen, and excess of carbon dioxide. Conversely, we believe that operative cardiac disturbances, including cardiac arrest, can be largely prevented by the use of light anesthesia. It follows that greater safety during cardiac surgery per se is assured.

We do not advocate the use of antiarrhythmic drugs for the prime purpose of preventing cardiac arrhythmias during anesthesia. We use these drugs preoperatively only for the established medical indications irrespective of anesthesia and surgery. As we have stressed previously,[1] these drugs are not entirely pure in their behavior because of their well-known toxic side-effects. Due to the low incidence of ventricular irritability during light anesthesia with nitrous oxide, we can avoid the prophylactic use of quinidine and procainamide hydrochloride prior to anesthesia. The safety of their prophylactic use has not been established. These drugs merely serve to cover up the potentially harmful insults of deep anesthesia. It is preferable to use the techniques of light anesthesia.

During light anesthesia, because of the excellent cardiovascular homeostasis, it is rarely necessary to use vasoconstrictor drugs in order to maintain an adequate blood pressure. If possible, it is preferable to avoid use of the pressor amines during general anesthesia because much remains to be learned about the constrictor actions of these drugs and also about the sensitization of the myocardium, especially in patients with coronary artery disease. These agents have also been advocated for their inotropic action on the myocardium depressed by ether when reflex adrenal response is inadequate.[2] This is not a problem during anesthesia with nitrous oxide in which myocardial contractility is not affected.

We have also observed that blood transfusion requirements are less in light anesthesia than in deeper levels in which the blood pressure is disturbed through myocardial depression, loss of vasomotor tone, and loss of integrity of the capillary bed. We have found the adrenal response to be quite adequate in even the most cachectic patients. It is seldom necessary to resort to the use of intravenous therapy with hydrocortisone during light anesthesia with nitrous oxide. We believe that in many instances poor-risk patients with semblance of adrenal exhaustion are given adrenal cortical solutions intravenously. Actually, the real factors responsible for the hypotension are the depth of anesthesia, hypoxia, and hypercapnia. These factors should be ruled out before resorting to intravenous therapy with hydrocortisone, which can produce a wide variety of responses, many undesirable.

Our observations of blood pressure during emergency surgery on critically ill patients in shock have demonstrated that anesthesia with nitrous oxide interferes minimally with the integrity of the peripheral vascular bed. Hershey and co-workers have demonstrated that the intrinsic tone, vasoconstriction, vasomotion, and reactivity of the peripheral vascular bed are more seriously deranged during deep anesthesia.[3] Patients who are in profound shock from severe infections or marked blood loss are especially vulnerable in deep anesthesia.

Many critical readjustments in body physiology take place at the end of anesthesia and surgery, and also in the immediate postoperative period. There is a change in the blood carbon dioxide level, and car-

diac irritability may be high. It has been suggested that cardiac arrest occurring during this period is probably intimately associated with deep anesthesia occurring toward the conclusion of the operation.[15] These factors again emphasize the value and safety of maintaining throughout the operation a light plane of anesthesia with a nontoxic drug like nitrous oxide. After light anesthesia, the patient awakens quickly and cooperates early by breathing deeply and coughing effectively, thereby preventing pulmonary complications. The blood pressure, too, follows a stable course in the immediate postanesthesia interval.

It has been stated that in some patients the muscle-relaxant drugs produce a fall in blood pressure due to the release of histamine or to a sympathetic ganglionic blockade. A recent survey suggests that the "curare" group of drugs may show an inherent toxicity and may contribute to the death of a considerable number of patients through circulatory collapse.[17] Our studies and experiences with the poorest of risks have been entirely different. We believe that these untoward side-effects of the muscle relaxants are related to concomitant deep anesthesia and are no problem during light anesthesia with nitrous oxide.

Summary and Conclusions

As a result of 10 years' experience with light analgesia with nitrous oxide—oxygen—curare in "poor-risk" patients undergoing major surgery, we found that electroencephalographic studies in patients given these anesthetics showed no significant changes from those of the wakeful state, documenting the extremely light level of anesthesia. Cardiovascular function was well maintained and depression of blood pressure and autonomic reflex disturbances were minimal. Disturbances of cardiac rate, rhythm, and conduction were infrequent. The incidence of vagotonia, ventricular irritability, and cardiac arrest was low. Full respirations were readily maintained. Breath holding, vomiting, laryngospasm, and bronchospasm were not problems. Patients with pulmonary insufficiency tolerated well this type of anesthesia. Blood gas analyses showed arterial blood oxygen saturation to be well maintained. Preliminary pCO_2 studies showed excellent elimination of carbon dioxide. Untoward cardiovascular effects of the muscle-relaxant drugs were not observed during light anesthesia with nitrous oxide. From these data we have concluded that in the "poor-risk" group the depth of anesthesia is of great importance. The cardiovascular dangers inherent in autonomic inbalance, reflex stimuli, lack of oxygen, and excess of carbon dioxide increase with the depth of anesthesia. The lighter the anesthesia, the more the patient is protected by the compensatory mechanisms of the wakeful state. Utilizing analgesia with nitrous oxide—curare, we have been able to carry out prolonged procedures safely on elderly or debilitated patients who would have been rejected for this type of surgery only a few years ago. Thus, the operation may be more deliberate, extensive, and definitive.

2 Maynard St. (Dr. Heller).

This investigation was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service, and in part by the Hitchcock Foundation, Hanover, N. H.

Technical assistance in this study was given by Kathleen Larkin, R.N., Dorothy Donnelly, and Krista Jensen.

References

1. Heller, M. L.; Nyboer, J., and Storrs, R. C.: Nitrous Oxide–Oxygen–Curare Anesthesia for Geriatric Patient: Electrocardiographic Study, Anesth. & Anal. **34**: 121-150 (May-June) 1955.

2. Brewster, W. R., Jr.; Isaacs, J. P., and Anderson, T. W.: Depressant Effects of Ether on Myocardium of Dog and Its Modification by Reflex Release of Epinephrine and Nor-Epinephrine, Am. J. Phys. **175**: 399-414 (Dec.) 1953.

3. Hershey, S. G.; Zweifach, B. W., and Rovenstine, E. A.: Effects of Depth of Anesthesia on Behavior of Peripheral Vascular Bed, Anesthesiology **14**: 245-254 (May) 1953.

4. (*a*) Harris, T. A. B.: The Mode of Action of Anaesthetics, Edinburgh, Scotland, E. & S. Livingstone, Ltd., 1951, pp. 554-595. (*b*) Burstein, C. L.: Fundamental Considerations in Anesthesia, New York, the MacMillan Company, pp. 63-73, 1949.

5. Clement, F. W.: Nitrous Oxide–Oxygen Anesthesia, ed. 3, Philadelphia, Lea & Febiger, 1951.

6. Courtin, R. F.; Bickford, R. G., and Faulconer, A., Jr.: Classification and Significance of Electro-Encephalographic Patterns Produced by Nitrous Oxide–Ether Anesthesia During Surgical Operations, Proc. Staff Meet., Mayo Clinic **25**: 197-206 (April 12) 1950.

7. Artusio, J. F., Jr.: Ether Analgesia During Major Surgery, J.A.M.A. **157**: 33-36 (Jan. 1) 1955.

8. Root, W. S., and McAllister, F. F.: Circulatory Responses of Chronic Spinal Dogs to Ether Anesthesia, Am. J. Physiol. **134**: 65-70 (Aug.) 1941.

9. Fine, J.: Etiology and Mechanisms of Shock: V. Irreversible Shock, in Symposium on Shock, Army Medical Service Graduate School, Washington, D.C., 1951, pp. V-1 to V-15.

10. Adriani, J.: The Pharmacology of Anesthetic Drugs: A Syllabus for Students and Clinicians, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1952.

11. Murtagh, J. A., and Campbell, C. J.: Laryngeal Spasm, Laryngoscope **64**: 154-171 (March) 1954.

12. Peters, R. M.: Relationship Between Per Cent of Carbon Dioxide in Inspired Air and Degree of Bronchoconstriction, Ann. Surg. **142**: 461-468 (Sept.) 1955.

13. Wasmuth, C. E., and Hale, D. E.: Changing Concepts of Anesthesia Depth, Cleveland Clin. Quart. **21**: 46-53 (Jan.) 1954. Footnotes 1 and 7.

14. Young, W. G., Jr.; Sealy, W. C.; Harris, J. S., and Botwin, A.: Effects of Hypercapnia and Hypoxia on Response of Heart to Vagal Stimulation, Surg., Gynec. & Obst. **93**: 51-55 (July) 1951.

15. Young, W. G., Jr.; Sealy, W. C., and Harris, J. S.: Role of Intracellular and Extracellular Electrolytes in the Cardiac Arrhythmias Produced by Prolonged Hypercapnia, Surgery **36**: 636-649 (Sept.) 1954.

16. Miller, F. A., and others: Respiratory Acidosis: Its Relationship to Cardiac Function and Other Physiologic Mechanisms, Surgery **32**: 171-183 (Aug.) 1952.

17. Beecher, H. K., and Todd, D. P.: Study of Deaths Associated with Anesthesia and Surgery Based on Study of 599,548 Anesthesias in 10 Institutions 1948-1952, Inclusive, Ann. Surg. **140**: 2-35 (July) 1954.

Treatment of Acute Leukemia.—Folic acid antagonists, the purine antagonists, and the steroid hormones are clearly of value in the treatment of human acute leukemia. The choice of what agent to employ initially in the therapy of acute leukemia, however, is dependent, at least in part, on the age of the patient. A high rate of initial remission in children with acute leukemia can be obtained with cortisone or corticotropin but when relapse occurs, a second remission rarely can be induced by the readministration of either compound. In such instances, repeated remissions may be observed following treatment with either the purine or the folic acid antagonists. In adults having acute leukemia, a higher rate of initial remission can be produced with 6-mercaptopurine than with the antifolic acid compounds or the steroid hormones. Hence 6-mercaptopurine would seem the drug of choice to be used initially in the adult. In acute leukemia in humans the existence of or eventual development of resistance to antileukemic agents seriously limits the possibility for adequate control of the disease. For this reason, various combinations of chemotherapeutic agents have been utilized in the hope that subsequent remissions could be obtained in drug resistant patients. It was shown by Burchenal (and later observed by the authors) that the simultaneous administration of azaserine and 6-mercaptopurine will induce remission in some patients with acute leukemia in whom a resistance to 6-mercaptopurine alone has developed.—B. E. Hall, M.D., F. M. Willett, M.D., T. V. Feichtmeir, M.D., E. B. Reed, M.D., and W. F. Dowling, M.D., Current Trends in Cancer Chemotherapy, *California Medicine*, January, 1956.

CLINICAL STUDIES ON A NEW CARDIAC GLYCOSIDE, ACETYLDIGITOXIN

Shantilal J. Shah, M.D., Shirley Rubler, M.D.
and
Raymond E. Weston, M.D., Ph.D., New York

• *Acetyldigitoxin was used in 80 patients with heart failure of varying degree and causation. For initial digitalization, 1.5 to 2 mg. was given by mouth in divided doses over a 24-hour period; for maintenance, 0.1 mg. was generally given by mouth once or twice daily. Intravenous administration was tried in a few patients, and the maintenance dose by this route was found to be about two-thirds of the oral maintenance dose.*

Anorexia, nausea, and electrocardiographic changes characteristic of digitalis overdosage were observed in 21 sicker patients in whom administration was continued deliberately to the point of therapeutic response or toxic effect. These subjective and objective signs of toxicity generally subsided within 24 to 72 hours. The promptness of their disappearance is an advantageous property of acetyldigitoxin.

Many reports [1] have appeared that document extensive European clinical trials with acetyldigitoxin (Acylanid), a new purified cardiac glycoside prepared first by Stoll and Kreis [2] by the enzymatic cleavage of a glucose molecule from lanatoside A, the glycoside derived from Digitalis lanata. However, the few published American studies [3] on this agent involved relatively small series of patients. The present paper reports selected observations on a larger number of cardiac patients, some of whom have been maintained on therapy with acetyldigitoxin for almost two years. The data provide the basis for a therapeutic evaluation of the new compound that confirms the clinical impressions of European investigators but establishes somewhat lower dosage requirements.

Methods and Materials

The subjects of the study were 80 patients, all but 4 of whom were hospitalized at Montefiore Hospital. Seventy-nine had clinically well-documented cardiac disease on the following etiological bases: rheumatic fever 35, hypertensive or arteriosclerotic heart disease 31, and other causes 14, including congenital heart disease, chronic constrictive pericarditis, chronic myocarditis of unknown etiology, and hyperthyroidism. One patient was a 44-year-old man without known heart disease who developed auricular fibrillation with a rapid ventricular rate 12 days after a previously uneventful right pneumonectomy for a bronchogenic carcinoma.

Ages of the subjects ranged from 5 to 85 years; 21 were younger than 40 years, 31 were from 40 to 60 years, and 28 were older than 60 years of age. All the cardiac patients exhibited objective or subjective signs of cardiac failure of varying degrees, including exertional dyspnea and tachycardia, orthopnea, rales, pleural effusion, peripheral edema, hepatomegaly, ascites, increased venous pressures, and/or prolonged circulation times. In regard to the basic cardiac rhythm, 34 had sinus rhythm, 45 auricular fibrillation, and one auricular flutter.

Twenty patients were studied on the cardiovascular metabolic research ward, where it was possible to obtain not only rigid control of the fixed food and fluid intakes and complete collections of urine and stools for balance measurements but also accurate apical rates and frequent electrocardiograms. Patients on the regular, as well as the metabolic, wards were maintained on a low-sodium intake (15 to 20 mEq.). Generally, as has been the practice on this service for some time,[4] whenever doses of digitalis were either being increased to, or maintained near, the point of toxicity, 45 to 120 mEq. of a palatable preparation of organic potassium salts was given orally in divided doses. Such doses reduce the incidence of electrocardiographic manifestations of "digitalis toxicity," which otherwise might reflect not overdosages of digitalis but the myocardial potassium depletion occurring in congestive failure spontaneously or after administration of diuretics.[5] Mercurial diuretics were given as indicated. If diuretic response was poor, mercurial injections were preceded by three or four days of treatment with 6 to 9 gm. of ammonium chloride daily, and followed two hours later by the slow intravenous injection of 0.5 gm. of aminophylline.[6] Body weights were recorded daily, and repeated venous pressure and arm-to-tongue circulation times were determined with dehydrocholic acid (Decholin).

Three general types of observations on acetyldigitoxin therapy were collected. In 18 patients who were previously not receiving any digitalis preparation, digitalization was achieved with divided doses of acetyldigitoxin orally for 10 to 148 hours. In the 62 previously digitalized patients, of whom 39 had been maintained for a long period on therapy with digoxin, 15 on therapy with digitoxin, 6 on therapy with digitalis leaf, and 3 on therapy with gitalin (Gitaligin), the equivalent daily maintenance dose of acetyldigitoxin orally was first established. Then, in any patients whose digitalization was not considered to be optimal, increased doses (0.1 or 0.2 mg. two to four times daily) of acetyldigitoxin were given until either a better therapeutic response or evidence of digitalis intoxication was obtained (see below). If under these circumstances only anorexia, nausea, malaise, or weakness were noted, either increased or maintenance dosage schedules were continued; but, once there was electrocardiographic evidence (prolonged PR interval, Wenckebach phenomenon, auricular fibrillation, or ventricular premature contractions) of intoxication,

From the Medical Division, Montefiore Hospital.
Dr. Shah is a Fulbright Exchange Fellow from Bombay, India.

which did not subside when increased doses of potassium salts were given orally, digitalis therapy was discontinued and repeated electrocardiograms were taken to determine how long the abnormalities persisted. Then, either the previous or a lower daily maintenance dosage schedule, which did not produce signs of toxicity, was instituted. In a few patients after establishing the maintenance dose orally, daily doses were given intravenously to compare the two routes of administration.

Results

Initial Digitalization.—Table 1 summarizes the pertinent clinical data and the doses of acetyldigitoxin orally required for initial digitalization and subsequent maintenance in the 18 undigitalized subjects. Generally, an initial dose of 0.8 to 1.2 mg. of acetyldigitoxin was followed by 0.4-mg. doses at four-hour to six-hour intervals until optimal therapeutic response

TABLE 1.—*Doses of Acetyldigitoxin Required for Initial Digitalization from 10 to 148 Hours and Subsequent Maintenance in Eighteen Patients*

Case No.	Age	Sex	Etiology*	Cardiac Rhythm	Initial Digitalization		Daily Maintenance Dose, Mg.
					Dose, Mg.	Time, Hr.	
1.	43	F	HCVD	Sinus	1.8	10	0.1, b.i.d.
2.	41	F	RHD	Sinus	1.6	24	0.1, b.i.d.
3.	50	F	RHD	Sinus	1.8	24	0.1, q.i.d. or b.i.d.
4.	52	F	HCVD	Sinus	2.0	24	0.1, b.i.d.
5.	37	F	RHD	Sinus	2.2	24	0.1, b.i.d.
6.	44	M	Lung Cancer	AF†	2.2	24	.....
7.	85	F	AsHD	AF	2.4	24	0.1, b.i.d.
8.	63	F	HCVD	AF	2.4	48	0.1, b.i.d.
9.	43	F	RHD	Sinus	2.4	48	0.1, b.i.d.
10.	36	F	RHD	Sinus	2.5	48	0.1, b.i.d. or q.i.d.
11.	72	F	AsHD	Sinus	2.8	48	0.1, b.i.d.
12.	65	F	AsHD	Sinus	2.8	60	0.1, b.i.d.
13.	5	M	CHD	Sinus	0.075	72	0.025, b.i.d.
14.	68	M	AsHD	Sinus	2.8	72	0.1, q.i.d.
15.	57	F	CHD	Sinus	3.0	72	0.2, b.i.d.
16.	29	F	RHD	Sinus	2.8	120	0.1, b.i.d.
17.	45	F	RHD	AF	3.2	120	0.1, b.i.d.
18.	52	F	CUP	Sinus	4.8	148	0.1, b.i.d.

* HCVD = hypertensive cardiovascular disease, RHD = rheumatic heart disease, AsHD = arteriosclerotic heart disease, and, CUP = chronic constrictive pericarditis.
† AF = auricular fibrillation.

or evidence of intoxication was elicited. In all 18 patients tachycardia was present; consequently, the pulse rate served as an index of the myocardial response to digitalization, particularly in the 14 patients with sinus rhythm, whose tachycardia was due to cardiac failure. Thus, reduction of the heart rate to 65 to 75 per minute without signs of overdosage generally reflected clinical improvement, as manifested by increased diuresis or decrease in dyspnea, fatigue, rales, peripheral edema, hepatomegaly, venous pressure, and/or circulation time. Therefore, when the pulse rate had fallen to 70 or less per minute, digitalization was considered to be adequate and maintenance therapy was begun.

The ranges of the total dose required for adequate digitalization with acetyldigitoxin given orally over the several time intervals studied were as follows: in 24 hours (seven patients), 1.8 to 2.4 mg.; in 48 hours (four), 2.4 to 2.8 mg.; in 60 to 72 hours (three), 2.8 to 3.0 mg.; and in 120 to 144 hours (three), 2.8 to 4.8 mg. In the 5-year-old boy with congenital heart disease, the comparable dose given over a 72-hour period was 0.675 mg., or 0.048 mg. per kilogram of body weight. If these individual initial digitalization doses are corrected by subtracting the subsequently established maintenance doses, as suggested by Hejtmancik and Herrmann,[7] the net digitalization dose over 24 hours is from 1.5 to 3.6 mg., with an average of 2.2 mg. for the 17 adults, or 2 mg. if the patient receiving the highest dose (case 18, table 1) is omitted.

The ratio between the subsequent maintenance dose given orally and the initial corrected 24-hour digitalization dose may reflect the daily rate of dissipation or the fraction of therapeutically active glycoside in the body that must be replaced each day. In these 18 patients the calculated average rate of elimination was 9.42% per day (range 4 to 18.2%). This rate is considerably slower than that reported by Löffler and others,[1c] who calculated an average daily rate of elimination of 14% of the initial dose of acetyldigitoxin in 22 patients digitalized and later maintained on the preparation intravenously. This discrepancy may reflect some difference either in the two routes of administration or in the criteria of adequate digitalization, which would affect the respective initial or maintenance doses.

Digitalization orally with fractional doses makes it more difficult to assay the rate of absorption or the time required to achieve initial and maximal therapeutic effects. However, the digitalization of one patient (case 6, table 1) who developed auricular fibrillation in 12 days after a pneumonectomy and of another patient (case 8, table 1), a 63-year-old hypertensive woman who developed auricular fibrillation 8 days after excision of the right middle lobe for benign atelectasis and fibrosis, provides some interesting data. Four hours after giving an initial 1.2-mg. dose of acetyldigitoxin there was a reversion to sinus rhythm in the patient in case 6, and his ventricular rate dropped from 200 to 100 per minute. His rhythm remained regular, and, after he received an additional 1 mg., his heart rate fell to below 80 per minute within 24 hours. Similarly, two hours after receiving orally an initial dose of 0.8 mg. of acetyldigitoxin, there was a reversion to sinus rhythm in the patient in case 8 and her ventricular rate fell from 170 to 190 to 100 per minute. She received two 0.4-mg. doses in the next 18 hours, and her pulse rate fell first to 80 and then, after receiving 0.8 mg. more, to 72 per minute by the end of a 48-hour period of digitalization. The total dose of 2.4 mg. given to this patient may have been excessive, inasmuch as she complained of some anorexia and slight nausea later in the day; however, when glycoside was omitted for 24 hours, she felt perfectly well and had no further difficulty later on a maintenance dosage schedule of 0.1 mg. twice daily.

Daily Maintenance Dosage.—In the 62 previously digitalized patients and in 17 of the 18 initially digitalized, the daily maintenance dose of acetyldigitoxin was established. In patients considered previously satisfactorily digitalized on the basis of clinical condition and the absence of signs or symptoms of intoxication, the daily dose of acetyldigitoxin required to maintain this status was determined by trial and error. When the previous digitalization was considered either inadequate or excessive, the daily doses of acetyldigitoxin were cautiously increased or decreased until

a better clinical response was achieved (as described above) before instituting maintenance therapy. As the data in table 2 indicate, the daily maintenance doses of acetyldigitoxin ranged from 0.1 to 0.4 mg. in the adult patients. Generally, the daily dose was divided, 0.1 mg. being given one, two, three, or four times daily, or on alternate days in those patients listed as receiving 0.15 or 0.25 mg. The majority of patients were on maintenance therapy of 0.1 mg. once or twice daily.

Once established, the daily dose usually remained the same over many months. However, at times, as with other digitalis preparations, changes in the patient's clinical status made it necessary to make appropriate adjustment in the daily dose. Often, the gradual cardiovascular deterioration of chronic congestive failure leads to insidious escape from previous adequate digitalization. When this occurred in the present studies, increasing congestive failure was often presaged by rising cardiac rates. Therefore, otherwise inexplicable, persistent elevations in apical rates were considered as indications for supplementary doses (0.1 or 0.2 mg.) of acetyldigitoxin, one to four times daily,

TABLE 2.—*Daily Dose of Acetyldigitoxin, Effect on Apical Rate, and Incidence of Intoxication in Eighty Patients*

	Daily Maintenance Dose, Mg.						Decrease in Apical Rate			Signs of Intoxication	
	0.05	0.1	0.15	0.2	0.25	0.3	0.4	None	<20	>20	None	Gastrointestinal	Electrocardiographic
No. of Patients*	1	32	4	34	1	5	2	41	13	26	59	11	20

* Dose for one patient not determined.

depending upon the urgency of the situation. If fluid accumulation occurred despite satisfactory digitalization, mercurial diuretics were given, preceded by ammonium chloride administration and followed by aminophylline injections. Once satisfactory redigitalization was achieved or signs of intoxication were elicited, the old or a new, higher maintenance dosage schedule was instituted.

After weeks on a constant dosage schedule, occasional patients exhibited signs of digitalis toxicity, such as anorexia, nausea, and arrhythmias, which necessitated reduction of their daily dose (see below). In hospitalized patients with very severe congestive failure, in whom satisfactory cardiac response with any preparation could be obtained only by digitalizing almost to the point of toxicity, each dose was ordered separately after carefully checking cardiac rate and rhythm by taking apical rates or electrocardiograms, as indicated. Once satisfactory control was established in such patients, supplemental doses of acetyldigitoxin were usually needed only at weekly or biweekly intervals, unless some acute infection or other complication developed that increased body metabolic demands.

Apical rate did not change significantly in 41 patients receiving acetyldigitoxin, chiefly in those previously well digitalized on other compounds. However, in the other 39 patients significant decreases in apical rate were observed after adequate digitalization was accomplished (table 2). In 13 cases, this decrease was less than 20 per minute, and, in 26, including most of the 18 acutely digitalized patients, it was greater than 20 per minute. It should be noted that these reductions in heart rate were achieved in patients with cardiac diseases varying etiologically from hyperthyroidism to diffuse myocarditis and chronic constrictive pericarditis and in the presence of regular sinus rhythm as well as auricular fibrillation.

Signs of digitalis toxicity were observed in 21 patients, in most of whom such intoxication was used as the end point of digitalization or redigitalization. In 11 patients gastrointestinal symptoms were noted, generally only anorexia or nausea except in 3 who finally developed vomiting when additional doses were given. In six of these patients the gastrointestinal symptoms preceded the more serious evidence of digitalis toxicity (cardiac arrhythmias), which developed when additional doses were given. In four, gastrointestinal symptoms and arrhythmias occurred simultaneously.

In 20 of the 80 patients, electrocardiographic evidence of intoxication was noted. Generally ventricular premature contractions (either occasional multifocal beats, bigeminy, trigeminy, or quadrigeminy) were observed, but there also occurred varying degrees of atrioventricular block (including simple prolonged PR intervals or the Wenckebach phenomenon) and in 2 patients auricular fibrillation, which reverted to sinus rhythm within 12 and 24 hours, respectively, when the patients were given additional organic potassium salt supplements orally. Almost uniformly, such signs subsided within 72 hours, and generally within 24 hours, when acetyldigitoxin was withheld and when the patient was placed on therapy with organic potassium salt supplements orally. Because of this rapid subsidence of toxic effects, maintenance doses and daily dissipation rates were established in several of these patients by determining repeatedly the minimal doses necessary, first, to reproduce electrocardiographic evidence of drug intoxication and, then, to maintain adequate digitalization without intoxication. In these studies reproducible signs, such as the Wenckebach phenomenon or ventricular premature contractions, generally subsided in 12 to 24 hours after the preceding, precipitating dose of acetyldigitoxin.

In table 3 a comparison is made between the daily dosages of acetyldigitoxin and digoxin or digitoxin required to maintain satisfactory digitalization in this series of patients. Inspection of the data reveals that daily doses of 0.1, 0.2, and 0.3 mg. of acetyldigitoxin are equivalent to 0.25, 0.5, and 0.75 mg. of digoxin respectively. In other words, in 33 of the 39 patients maintained on therapy with both of these glycosides, 0.1 mg. of acetyldigitoxin was equivalent to 0.25 mg. of digoxin. In the patients who had previously been receiving digitoxin, the dose of the two glycosides was the same in 9 of 15, whereas 6 previously maintained on 0.1 mg. of digitoxin daily required 0.1 mg. of acetyldigitoxin twice daily. However, because of the small number of patients observed in this study, it is not possible to establish ratios between the doses of digitoxin, digitalis leaf, or gitalin and the equivalent dose of acetyldigitoxin.

Comment

Certain characteristics of the purified glycosides, which otherwise have the same effects on the failing heart as the Galenic preparations of digitalis, have led to their increasing clinical use in recent years. The chemical purity of the crystalline materials not only

permits gravimetric determination of potency but also insures reproducibility and constancy of both absorption and therapeutic effect. Moreover, when oral administration is contraindicated, preparations of most of these products, including those with short latent periods that may also be used for rapid digitalization intravenously, are available for parenteral use.

Therapeutically, the glycosides that have been purified since Nativelle first developed digitoxin [8] differ only with respect to speed of action, duration of therapeutic and/or toxic effects, and presumably ratio of the therapeutic to the toxic dose. For example, it has been well established [9] that digitoxin achieves a maximal effect and is excreted much more slowly than is digoxin, whereas it has been reported [10] that the ratio of the therapeutic dose to the toxic dose for gitalin is only one-third in contrast to approximately two-thirds for the other commonly used glycosides. In an effort to find a glycoside with less persistent toxicity and a wider therapeutic margin than digitoxin, Stoll and Kreis [2] prepared acetyldigitoxin by enzymatic cleavage of a glucose molecule from lanatoside A. Despite its close chemical relationship to digitoxin, animal studies suggested that, although the gastrointestinal absorption and cardiac effects of the two glycosides were equivalent, the excretion or dissipation of toxic effects of acetyldigitoxin occurred much more rapidly.[11]

TABLE 3.—*Comparison Between Daily Doses of Acetyldigitoxin and Previous Maintenance Doses of Digoxin or Digitoxin*

Previous Dose of Digoxin	No. of Patients on Given Mg. Dosage Schedules of Acetyldigitoxin			
	0.1	0.2	0.3	0.4
0.25	18	3	...	...
0.50	2	11	...	...
0.75	...	...	4	1
Previous Dose of Digitoxin				
0.1	5	6	...	...
0.20	...	4	...	...

The present studies confirm the results of the extensive European [1] series and the smaller series of American clinical trials [3] demonstrating that, like digitoxin, acetyldigitoxin given orally is well tolerated and readily absorbed but that it achieves a near maximal therapeutic effect sooner and, in patients digitalized to the point of drug intoxication, is excreted much more rapidly than is digitoxin. However, analysis of the data suggests that doses orally given for both initial digitalization and subsequent maintenance therapy are somewhat lower than those employed abroad. Thus, an optimal therapeutic response without evidence of drug intoxication probably can be achieved and maintained in most patients by giving 1.5 to 2 mg. by mouth in divided doses over 24 hours, as other American reports [12] indicate, followed by later doses of 0.1 mg. orally once or twice daily. On such schedules, except in very sick patients whose doses often must be gradually increased until either therapeutic response or drug intoxication is achieved, subjective or objective evidence of overdigitalization is minimal.

Of great significance is the fact that, in patients receiving acetyldigitoxin in contrast to digitoxin, signs of intoxication subside quickly, generally within 24 and almost invariably within 72 hours. This rate of subsidence of induced intoxication is greater than anticipated in view of the daily dissipation rate of approximately 10%, calculated by comparing the daily maintenance dose orally with the effective digitalization dose orally in 17 patients in the present series. The higher 14% dissipation rate in 27 patients who were digitalized and maintained on acetyldigitoxin administered intravenously by Loeffler and others [1c] may reflect the transiently higher blood levels and consequently more rapid excretion of acetyldigitoxin resulting from intravenous rather than oral administration. Furthermore, in the light of the 50 to 60% therapeutic-toxic dose ratio reported for acetyldigitoxin,[1c] the relatively greater safety of the oral route may have led us to give initial digitalizing doses somewhat in excess of those required for optimal therapeutic response. With the relatively lower maintenance doses, the excess would be rapidly excreted, leaving in the body an undeterminable but smaller quantity of active glycoside, the correct denominator for calculating dissipation rate.

This relatively rapid disappearance of the objective and more dangerous signs of digitalis intoxication in patients receiving acetyldigitoxin has been abundantly confirmed. It is equivalent in our experience to that observed in patients maintained on therapy with digoxin, a rapidly dissipated glycoside. Lown and Levine [13] have properly emphasized that rapidly eliminated compounds are the cardiac glycosides of choice in patients with advanced heart failure. In such patients, despite their reduced myocardial threshold to the toxic effects of digitalis, increasing doses must often be given until either a therapeutic response or intoxication is achieved, and subsequent maintenance therapy, as in many of the patients in the present series, frequently borders on production of toxic effects. Like digoxin, acetyldigitoxin is well suited for such therapeutic regimens, in which 0.1 mg. generally can replace 0.25 mg. of digoxin.

A rapid rate of dissipation of the toxic effects of a cardiac glycoside ordinarily implies a rapid escape from the therapeutic effect too; however, it has been our experience that adequate digitalization may be readily maintained with both digoxin and acetyldigitoxin outside the hospital, if the patient is instructed to take the prescribed dose one or more times daily, as indicated, depending on pulse rate and symptomatology. Periodic office or clinic checks on the apical rate and clinical status of a patient with fibrillation serve as further guides to the therapy. It is of interest that, in some patients, generally with sinus rhythm but occasionally with auricular fibrillation, cardiac compensation and normal heart rates at rest may persist for three to four weeks after the oral administration of these more rapidly excreted glycosides is discontinued. Whether this persistent therapeutic response reflects myocardial fixation of some fraction of the digitalis body is not known. Nevertheless, it presents a striking contrast to the rapid disappearance of toxic effects when these same patients are overdigitalized.

Summary and Conclusions

In a series of 80 patients with heart failure of varying degree and etiology, with regular sinus rhythm as well as with auricular fibrillation, acetyldigitoxin (Acylanid) has been found to be a highly satisfactory

cardiac glycoside. The data suggest that in most patients initial digitalization can be achieved by giving 1.5 to 2 mg. in divided doses by mouth over a 24-hour period, following which therapeutic response without evidence of intoxication or escape from digitalization generally may be maintained by doses of 0.1 mg. orally once or twice daily, as indicated. Since but two-thirds of the dose given orally is absorbed from the gastrointestinal tract, the digitalizing and maintenance doses given intravenously are proportionately lower. In patients with severe congestive failure, whose maintenance digitalization often borders on toxic levels, any induced objective and subjective signs of overdigitalization with acetyldigitoxin usually subside within 24 to 72 hours. In this respect, as in others, the newer glycoside therapeutically resembles digoxin rather than digitoxin.

210th Street and Bainbridge Ave. (67) (Dr. Weston).

This study was supported in part by grants from the National Heart Institute, U. S. Public Health Service; Eli Lilly & Company, Indianapolis; G. D. Searle & Co., Chicago; and Sandoz Pharmaceuticals, Hanover, N. J.

The acetyldigitoxin used in this study was supplied as Acylanid by Sandoz Pharmaceuticals, Hanover, N. J.

Drs. Helen B. Horowitz, Marian C. Isaacs, Alvin Essig, Donald Gibbons, and Robert Rosenblum, Research Fellows on the Cardiovascular and Metabolic Research Service, assisted in this study.

References

1. (*a*) Trolliet, J.; Conne, G., and Dreyfuss, R.: Résultats thérapeutiques obtenus avec l'acetyl-digitoxine-Sandoz, Praxis **42**: 310, 1953. (*b*) Häusler, H. P., and Hörtnagl, W.: Klinisch-experimentelle Untersuchungen über die Herz- und Kreislaufwirksamkeit eines neuen Digitalis-Reinglykosides (Acetyldigitoxin), Wien Klin. Wchnschr. **65**: 473, 1953. (*c*) Löffler, W.; Esselier, A. F., and Forster, G.: Acetyldigitoxin: Clinical Observations on the Treatment of Patients with Advanced Congestive Heart Failure, Am. Heart J. **47**: 898, 1954.

2. Stoll. A., and Kreis, W.: Acetyldigitoxin-α und Acetyldigitoxin-β, Helvet. chim. acta **35**: 1318, 1952.

3. Zilli, A., and Luisada, A. A.: Effects of Acetyldigitoxin in Ambulatory Patients with Congestive Failure, Exper. Med. & Surg. **13**: 3, 1955. Maher, C. C., Jr., and Pullen, C. W.: Acetyldigitoxin—a New Cardiac Glycoside, Rocky Mountain M. J. **52**: 436, 1955. Clouch, R. B.; Hejtmancik, M. R., and Herrmann, G. R.: Clinical Studies of Acetyldigitoxin, Am. Heart J., to be published.

4. Hanenson, I. B.; Weston, R. E.; Grossman, J., and Leiter, L.: Symposium on Prolonged Illness: Pathogenesis and Treatment of Congestive Heart Failure, M. Clin. North America **37**: 643, 1953.

5. Lown, B.; Salzberg, H.; Enselberg, C. D., and Weston, R. E.: Interrelation Between Potassium Metabolism and Digitalis Toxicity in Heart Failure, Proc. Soc. Exper. Biol. & Med. **76**: 797, 1951.

6. Weston, R. E.; Escher, D. J. W.; Grossman, J., and Leiter, L.: Mechanisms Contributing to Unresponsiveness to Mercurial Diuretics in Congestive Failure, J. Clin. Invest. **31**: 901, 1952.

7. Hejtmancik, M. R., and Herrmann, G. R.: Clinical Study of Gitalin, A.M.A. Arch. Int. Med. **90**: 224 (Aug.) 1952.

8. Nativelle, C. A.: Sur la digitaline cristallisie, J. Pharmacie **9**: 255, 1869.

9. Batterman, R. C., and DeGraff, A. C.: Comparative Study on Use of Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure, Am. Heart J. **34**: 663, 1947.

10. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Therapeutic Range of Gitalin (Amorphous) Compared with Other Digitalis Preparations, Circulation **5**: 201, 1952.

11. Rothlin, E; Bircher, R., and Schalch, W. R.: Zur Pharmakologie des Acetyl-Digitoxin-α, Schweiz. med. Wchnschr. **83**: 267, 1953. Rothlin, E., and Bircher, R.: Pharmakodynamische Grundlagen der Therapie mit herzwirksamen Glycosiden, Ergebn. inn. Med. u. Kindesk. **5**: 457, 1954.

12. Footnotes 2 and 3.

13. Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954.

CURRENT CONCEPTS OF ACUTE ARTERIAL INJURIES

Edgar S. Brintnall, M.D., Robert C. Hickey, M.D.
Richard L. Lawton, M.D., Frederick D. Staab, M.D.
and
Samuel H. Walker, M.D., Iowa City

Restoration of circulation in patients with acute arterial injuries is the obligation of every surgeon who undertakes the definitive treatment of traumatic wounds. The general principles concerned in the treatment of arterial injuries are commonplace; basic techniques are not complicated.[1] It is no longer permissible for the surgeon to be prepared only to arrest hemorrhage and to ligate arteries when confronted with vascular injuries. Present-day knowledge demands that he carefully evaluate the injury and be aware of the sequelae of arterial ligation. The advantages to the patient of fully reestablished blood flow are so great that vascular restoration must be the rule in the treatment of wounds involving major arteries—restoration through direct vessel repair, by vessel homograft, or by relief of occluding extrinsic pressure.

The general principles of wound treatment obtain in wounds involving arteries as in other wounds. These include preoperative evaluation of extent of injury, proper débridement, prophylaxis against infection, treatment of associated injuries, and indications for wound closure, including primary or delayed wound closure, or closure by skin graft. The emergency control of hemorrhage by pack, pressure, or

From the Surgical Service, Veterans Administration Hospital, and the Department of Surgery, State University of Iowa, College of Medicine.

• *The first-aid tourniquet, though life-saving, should be removed as soon as it can be replaced by means such as clamps or packs that are less damaging to skin, muscle, nerves, and vessels. Ligation can result in impaired function even if no ischemia is evident; it should be done only in the smaller arteries distal to the popliteal in the leg or the brachial in the arm.*

Optimum results in the treatment of injured arteries depend on technical refinements. The six case histories here given illustrate (1) the danger of hematomas underlying dense fascia, (2) the good results obtained from end-to-end anastomosis when major arteries have been transected, (3) the successful averting of gangrene by using an arterial homograft to repair a 9-cm. gap, (4) the occasional need of repeated operation of recurrent thrombosis, (5) the feasibility of ligating small peripheral arteries, and (6) the successful use of a branching arterial homograft 16 cm. in length, with recovery from claudication and ischemic ulceration, 11 years after excision of an arteriovenous fistula in the thigh. The immediate restoration of arterial flow by using grafts avoids the delay thought necessary for the development of collateral circulation. It reduces the amount of functional impairment and exemplifies restorative as distinguished from ablative surgery.

tourniquet is well understood. These methods are important when used properly. The first-aid tourniquet should be removed as soon as possible and a pneumatic cuff apparatus applied. Deleterious tourniquet effects include direct pressure damage to skin, muscle, nerves and vessels, as well as indirect damage to tissues distally from prolonged circulatory deficit. Direct control of bleeding by pack, temporary ligature, or clamp often enables the physician to gain advantages for the patient without incurring tourniquet risks.

Hemorrhagic shock is best treated by restoration of blood volume with whole blood transfusions. Restoration of blood flow in larger arteries is preferable to ligation, even though the ligation might not be followed by gangrene. Significant circulatory deficit may result from ligation, even though no ischemia is evident. Ligation should be acceptable in general only in the smaller arteries distal to the popliteal artery in the lower extremity and distal to the brachial artery in the upper extremity. Ligation of the axillary, brachial, and superficial femoral arteries is seldom followed by gangrene, but disability follows. Extremity coldness, fatigability, and claudication are frequent. Interruption of autonomic nerve impulses by blocking drugs, by injection of local anesthetics, and by surgical ganglionectomy has proved disappointing. These are no substitute for restoration of blood flow through main arterial channels.

Localized severe spasm of a major artery at the site of direct injury from a fracture fragment or other contusing force is different. Such segmental artery spasm is of local cause, and local treatment is effective. If the segmental spasm is not associated with thrombosis, treatment consists of release of mechanical pressure on the artery (e.g., reduction of a displaced fracture fragment), application of warm saline solution packs, and topical application of cocaine solution or injection of procaine solution into the vessel adventitia. If the spasm is associated with traumatic thrombosis and/or intimal detachment, resection of the damaged segment is indicated, with blood flow reestablishment through an appropriate vessel homograft. Thromboendarterectomy is an unreliable method of treatment after trauma, as thrombosis will likely reoccur.

Subfascial hematoma is deceiving and dangerous. As subfascial tension increases from arterial hemorrhage and associated edema, arterial flow is progressively diminished in both major and collateral arterial channels. Tissue necrosis and, finally, gangrene result. Prompt relief of compartmental tension may be obtained by wide fasciotomy. Regional heparinization is attempted frequently during operation to prevent blood coagulation in the extremity distal to the site of arterial injury. The heparin solution is injected into the arterial tree in the direction of flow before beginning vascular repair or vessel homograft. This so-called regional heparinization may be largely mythical, but we are still using this technique. The small volume of solution must fail to fill and heparinize the peripheral arterial channels completely, and, further, the solution may soon be lost into the general circulation if even small collateral vessels are functioning. Anticoagulants are not used after operation except with special rare indications. Major vein ligation in the hope of enhancing tissue oxygenation in the presence of arterial deficit is not beneficial.

Technical Considerations

Success in the treatment of vascular injuries depends in a large part upon certain technical refinements. If ligation is required as a temporary expedient, it should be carried out close to the injury site to avoid damage that would add to the difficulties of subsequent definitive arterial repair. The results of surgery are excellent for acute arterial injuries if repair is accomplished within four to six hours. Artery repairs and grafts cannot succeed unless the distal

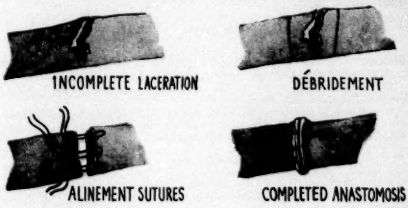


Fig. 1.—Treatment of localized artery injury by limited resection and direct end-to-end anastomosis.

portion of the arterial tree is unobstructed. Unless the repair is begun soon after the injury has occurred, blood clot is likely to exist in the vessel lumen on either one or both sides of the wound. Such clots must be gently and completely removed. Suction and milk-

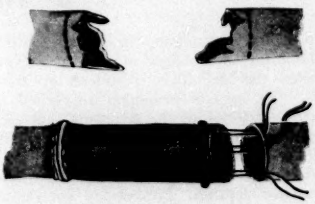


Fig. 2.—Treatment of an extensive artery wound by débridement of injured artery ends and restoration of continuity with a transplant.

ing techniques usually remove clots and do not cause intimal injury. Irrigation within the vessel combined with intermittent suction through a catheter often clears the artery of long string-like clots that previously resisted removal. A limited débridement of injured vessel is usually required to provide healthy tissue for repair. Frayed and contused vessel margin must be excised. Segmental resection of injured artery is occasionally required.

During artery repair, bleeding must be controlled in a manner not damaging to the vessel wall. If serrefine clamps are not available, nontraumatizing occlusion may be obtained by means of an encircling rubber band or Penrose drain, which is held snug with a hemostat. Every care should be exercised to avoid

traumatizing the arterial wall from within or from without. The most reliable and appropriate stitch for use in small and medium-sized arteries is the interrupted, intima-everting, flat-mattress suture method described by Jaboulay and Briau in 1896.[2] This technique is equally applicable to direct artery anastomosis and vascular hemograft (fig. 1 and 2). Intimal eversion and accurate suturing with 0000 and 00000 arterial nonabsorbable surgical suture provide a smooth lumen at the repair site, thus lessening the chance of intraluminal occlusion from blood clot. The interrupted suture technique minimizes anastomotic narrowing. A continuous suture is likely to result in a purse-string effect. The continuous vessel suture, interrupted at three or four sites, without intimal eversion is satisfactory for the aorta, where the lumen is large and the volume flow is great, but it is not appropriate for repair of smaller arteries such as the femoral.

Direct end-to-end anastomosis is performed when a limited mobilization of vessel ends can be accomplished without injury to important collateral channels. Excessive tension, however, upon the anastomosis line must be avoided. Arterial continuity is reestablished by vessel homograft where the graft is required to bridge a sizable gap, or to avoid excessive anastomotic tension, or to prevent injury to large collateral vessels from extensive mobilization of the injured artery. Vessel homografts should be of a appropriate caliber, as disproportion produces eddy currents that favor thrombosis.[5] Grafts are placed under slight tension, as this duplicates the normal situation and probably minimizes turbulence.

Fig. 3.—Ecchymosis, swelling, and arterial insufficiency following shotgun wound in left popliteal area.

When available, arterial homografts preserved by freeze-drying and stored at room temperature in vacuum tubes are used.[4] These homografts are well tolerated and lend themselves to easy technical handling. When autogenous vein must of necessity serve as the graft, its direction is reversed so that valves do not hinder blood flow. Because the vein dilates to about one and one-half to two times its usual caliber when subjected to arterial pressure, a vein smaller than the artery to be bridged must be selected. The long saphenous vein is readily accessible and is of a size reasonably appropriate for replacement of segments of popliteal, femoral, brachial, and axillary arteries.

The vessel segment repaired or grafted must be surrounded by viable uninfected tissue and must not be exposed to the exterior. It is preferable that the wound be closed completely after débridement and vascular repair. If the wound cannot or should not be closed, the vessel repair or graft must be covered by healthy tissues, for otherwise secondary hemorrhage and slough of grafted tissue occurs. Homografts must be nourished and invaded by reparative tissue from adjacent structures if they are to be successful. Usually an artery repair site can be buried conveniently in healthy muscle even though complete wound closure is not possible. In appropriate circumstances, a split-thickness skin graft will convert an open traumatic wound with loss of skin into a primary wound closure.

Illustrative Clinical Problems

Puncture Wounds of Major Artery with Subfascial Hemorrhage—Artery Repair and Fasciotomy.—A 22-year-old man sustained a .410 gauge shotgun wound of the left knee region on Nov. 30, 1954. Progressive swelling developed in the extremity. The day following the injury, coldness and cyanosis developed and the calf became painful and tender. At the time of hospital admission and operation, four days after the injury, the left lower extremity was cold, pulseless, mottled, cyanosed, and ecchymotic (fig. 3). Pellet wounds were evident on the medial aspect of the knee. Lumbar sympathetic block did not improve the circulation. Through a posterior incision, the popliteal space and the posterior fascial compartment of the leg were exposed widely. The calf musculature was hemorrhagic, edematous, and initially appeared lifeless. The popliteal artery and vein were in continuity. Upon relief of local pressure by fascial division and separation of muscles, blood coursed through the artery into its tibial and peroneal divisions and blood spurted from two puncture wounds in the popliteal artery. Fine arterial nonabsorbable surgical sutures were used to repair the small artery wounds. The exposed calf musculature regained a more normal color. An extensive fasciotomy of crural fascia was performed, extending as low as the ankle. Postoperatively, the proximal leg tissues showed signs of viability, while the distal portion of the leg and foot remained nonviable and became gangrenous. Leg amputation was performed 5 in. below the knee on Dec. 9, 1954, 10 days after the injury. Free bleeding was observed from the transected larger arteries, demonstrating the restoration of blood flow in these channels.

This patient lost his extremity from circulatory insufficiency due to the pressure deep to the crural fascia. The increased tension within the fascial compartment of the leg caused venous obstruction and finally such compression of arterial flow that the distal and most vulnerable part of the extremity became gangrenous. The small distal vessels became occluded by clot. There is little doubt that early fasciotomy and repair of popliteal artery puncture wounds would have saved the extremity.

Transection of Major Artery—Immediate Repair by Direct End-to-End Anastomosis.—A 26-year-old man was seen Aug. 20, 1955, one-half hour after he had been involved in an automobile accident. He had sustained an incised wound of the inner aspect of the right arm and a cerebral concussion. A makeshift tourniquet was in place on the upper right arm. There was severe hemorrhagic shock. Shock was controlled by administration of 2,000 cc. of whole blood and 500 cc. of plasma expander. Two hours after the injury, the wound was explored and débrided. The cleanly severed brachial artery was repaired by direct end-to-end anastomosis. The severed median nerve was repaired with perineural sutures of fine nonabsorbable surgical suture. The partially divided biceps muscle was repaired. The wound was closed in layers, and a plaster splint was applied. The patient's postoperative course was satisfactory. The arterial circulation was normal. Radial pulsations and those in the distal portions of the brachial artery were strong and equal bilaterally, but the median nerve function had not returned when the patient was last seen, one month after operation.

This case involved the technical problem of a cleanly divided brachial artery. It was probable that ligation of the artery would have been tolerated, as most of the small collateral arteries were uninjured. By artery repair, a hazard to function was not risked.

Extensive Major Artery Laceration and Impending Gangrene—Correction by Arterial Homografting and Fasciotomy.—A 20-year-old man sustained a .32 caliber pistol wound of the right lower quadrant of the abdomen on Nov. 12, 1955. An hour later at emergency laparotomy in another hospital the intestinal wounds were repaired and bleeding was controlled by ligation of the right external iliac artery; through a separate incision the right common femoral artery was ligated below the inguinal ligament. Increasing evidence of inadequate circulation in the right lower extremity developed, manifested by coldness below the knee, discoloration of foot and leg, inability to move the foot, and sensory loss in the leg and foot. At the time of hospital admission, Nov. 15, 1955, three days after injury, gangrene of the right foot and lower leg seemed imminent. The patient was unable to move the toes, and ankle and knee movements were limited by pain. The extremity was cold and swollen below the knee. The calf muscles were tense and painful to pressure. Skin sensation was diminished distal to the knee and absent in the foot and ankle. The foot and ankle presented a blotchy, bluish discoloration. No pulsations were palpable.

Operation was performed Nov. 15, 1955. A right oblique iliolumbar incision provided retroperitoneal exposure of the injured artery. A 3.5-in. segment of artery was missing. After the ligatures were released, a clot was removed from the proximal end of the artery and bleeding occurred from both open ends. The injured artery was excised to healthy arterial tissue. Continuity was reestablished by utilizing an appropriately sized freeze-dried, sterile artery homograft, which had been stored in a vacuum tube. Full arterial flow through the graft ensued. The intact accompanying vein was patent and was left so. Because of the clinical diagnosis of ischemic swelling of leg muscles, both the anterior and posterior leg compartments were opened widely by anterior and posterior crural fasciotomy. The muscles of these compartments were grayish, swollen, and avascular. The skin was closed over the anterior fasciotomy incision, but edema prevented closure of the long posterior skin incision.

The patient's postoperative course was excellent. There was a return of skin sensation. Normal color returned to the leg and foot except for the tips of three toes, which blackened and mummified and were débrided. The extremity became warm to touch, and swelling receded. The exposed calf muscle assumed a normal color and appearance. Circulatory improvement was gradual rather than abrupt. Four days after operation, strong pulsation was palpable in dorsal pedal and posterior tibial arteries. Secondary closure of calf skin was carried out Dec. 9, 1955, 24 days postoperatively. Motor function in the extremity recovered somewhat, but it was necessary to resect necrotic muscle in the anterior compartment on the 34th day after operation. At present the patient has weak dorsiflexion of the foot through peroneal musculature for which he uses a mechanical foot brace.

This case is of unusual interest because impending complete gangrene was prevented, near-normal circulation was restored, and functional partial recovery was brought about by crural fasciotomy and artery homograft three days after injury. The muscles in the anterior compartment are more vulnerable to vascular injury. Collateral circulation prevented thrombosis in most of the smaller distal vessels, otherwise gangrene would have become established in the foot and ankle despite the technical success of the artery grafting procedure. The good result may be due in part to fasciotomy, as well as to the late artery repair. The anticipated amputation was prevented.

Surgical Injury (Repeated Embolectomy) of Major Artery with Thrombosis—Segmental Resection and Arterial Homografting.—A 54-year-old man was hospitalized Oct. 30, 1955, because of congestive heart failure, syphilitic aortitis, and polycythemia. Appropriate treatment relieved the heart failure. On Nov. 8, 1955, symptoms and signs of embolism of the right femoral artery developed suddenly. At emergency operation an embolus was removed from the bifurcation of the right common femoral artery. Circulation was restored to the extremity. The source of the embolus was not determined. A program of long-term anticoagulant therapy was instituted. Subsequent successful arterial embolectomies were performed as follows: Nov. 17 (morning), left common femoral; Nov. 17 (afternoon), right common iliac; Nov. 20, right common femoral; and Nov. 21, right common femoral.

On Nov. 21, several hours after the last embolectomy, evidence of right femoral artery occlusion led to a fourth exploration of the vessel. A distinct embolus was not found, but the artery was clot-filled at the site of previous embolectomies. Thrombosis had occurred due to arterial injury from surgery and embolism. The vessel was temporarily repaired after clot extraction while an arterial homograft was prepared. Circulation in the extremity was restored, but one-half hour later, upon segmental excision of the injured artery, the segment was found rethrombosed. A 7-cm. segment of common and superficial femoral artery was resected, and the defect was bridged with a bifurcation arterial homograft. Restoration of circulation followed, through both superficial and deep femoral arteries. The patient did not develop further evidence of occlusion of peripheral vessels, but he died Dec. 2, 1955, 11 days after the last operation, from cardiac failure complicated by widespread mesenteric thrombosis. Postmortem injection of radiopaque solution into the right external iliac artery established radiographic proof of patency through all anastomoses.

Local artery thrombosis resulted from repeated traumas of embolism and embolectomy. Artery segments so injured require resection and replacement by healthy tissue. Indications for artery repair and grafting include operative injury as well as accidental injury incident to fractures and gunshot wounds.

Traumatic Arterial Aneurysm (Pulsating Hematoma) of Minor Artery—Ligation and Excision.—A 53-year-old man was struck on the left forearm by flying metal on July 31, 1955. At the time of injury, vigorous bleeding from a puncture wound was controlled by pressure. Three days after injury, a gradually enlarging mass at the injury site exhibited pulsation. On admission, Aug. 11, 1955, a subcutaneous pulsatile mass that was 2 cm. in diameter was found in the forearm overlying the radius distally. Radiographs revealed a small metallic object adjacent to the soft tissue mass. There was an adequate collateral circulation through the ulnar artery as determined by selective multiple arterial compression. The area was explored surgically Aug. 12, 1955, and a pulsating false aneurysm was removed by ligating the radial artery proximally and distally. The result was satisfactory.

False arterial aneurysm (pulsating hematoma) should be treated early. If an important artery is involved, it is repaired either by suture, by segmental excision and end-to-end anastomosis, or by segmental excision and graft replacement. In an instance of a minor artery (e.g., radial or ulnar artery), excision and ligation is usually adequate. Early treatment avoids rupture and ischemic damage of overlying or distal tissues.

Arteriovenous Aneurysm Treated by Excision, with Subsequent Ischemic Symptoms—Defect Bridged by Arterial Homograft.—A 31-year-old man sustained a gunshot wound of the left upper thigh in 1943. The resulting arteriovenous fistula was treated by quadruple ligation and excision in 1944. There were no marked ischemic symptoms until 1949, when swelling of the leg and ulceration of the heel occurred. Recurrent heel ulceration led to a cross-leg skin-flap transfer in 1952. Except for coolness of the left lower extremity and mild intermittent claudication, the patient remained well for three years more, after which time an ulcer on the left ankle developed and failed to heal. At hospital admission, Aug. 9, 1955, examination revealed pigmentation

of skin of the lower portion of the left leg and ankle and an ulcer that was 3 cm. in diameter above the medial malleolus. The left leg and foot were cool to touch as compared with the right, and no pulsation was palpable in arteries distal to the left groin. Arteriography revealed interruption of the left superficial femoral artery just below the deep femoral branch. The ulcer on the ankle failed to show healing after five weeks of treatment.

Operation was carried out Sept. 15, 1955, through a long incision on the thigh. The ends of the superficial femoral artery were located and were found to be patent. The gap in the artery was bridged with an arterial homograft, which had been preserved by freeze-drying. The graft measured 16 cm. in length. Immediate vigorous blood flow was observed to traverse the transplant. Postoperatively, arterial circulation in the left lower extremity was normal. Pulsation was evident in dorsal pedal and posterior tibial arteries. The ulcer healed promptly, claudication disappeared, and the extremity became warm.

This case demonstrates the disadvantage of ligation of major arteries. The arterial ligation was well tolerated initially, but the extremity was not normal subjectively. Coldness and mild claudication were annoying. Symptoms of arterial insufficiency increased and caused the patient to seek relief. It was fortunate that blood flow could be reestablished through the main arterial channel by a homograft 11 years after the artery ligation and excision. Arteriovenous fistula should be treated promptly by restorative rather than ablative methods. Immediate restoration of arterial flow avoids the delay thought necessary for the development of collateral circulation and avoids concomitant cardiac damage and damage to veins in the injured extremity.

Summary

Restoration of blood flow may be obtained in a variety of common arterial wounds by end-to-end anastomosis, graft interposition, or relief of extrinsic pressure. The advantages of a fully reestablished arterial flow are so great that vascular restoration should be the rule in the treatment of wounds involving major arteries. Success in treatment of vascular injuries depends on proper consideration of technical refinements.

References

1. DeBakey, M. E., and Simeone, F. A.: Battle Injuries of Arteries in World War II: Analysis of 2,471 Cases, Ann. Surg. **123**: 534-579 (April) 1946. Jahnke, E. J., Jr., and Seeley, S. F.: Acute Vascular Injuries in the Korean War: Analysis of 77 Consecutive Cases, ibid. **138**: 158-177 (Aug.) 1953.

2. Jaboulay, M., and Briau, E.: Recherches expérimentales sur la suture et la greffe artérielles, Lyon méd. **81**: 97-99 (Jan.) 1896.

3. Schmitz, E. J., and others: Influence of Diameter Disproportion and of Length on Incidence of Complications in Autogenous Venous Grafts in Abdominal Aorta, Surgery **33**: 190-206 (Feb.) 1953.

4. Taber, R. E.: Arterial Homografts, J. Iowa M. Soc. **44**: 472-473 (Oct.) 1954.

POSTMATURITY AND THE PLACENTAL DYSFUNCTION SYNDROME

Ralph H. Kunstadter, M.D.
and
Sidney E. Schnitz, M.D., Chicago

• *Postmaturity, taken as meaning a gestational age of 294 days or more, occurred 247 times in a series of 2,877 deliveries. Gestational age exceeded 299 days in 132 of these babies.*

The postmature group did not differ significantly, as to average weight and body length, from a group of 252 babies born after the 259th and before the 295th day. The postmature group did, however, include 11 infants with one or more clinical findings characteristic of a placental dysfunction syndrome: dry, scaling, parchment-like skin; staining of the skin and vernix caseosa; and poor tissue turgor, subcutaneous tissue wasting, or other evidence of recent weight loss. Four cases of this are described in some detail. In the full-term group, on the other hand, there was only one infant with any findings consistent with this picture.

Perinatal mortalities in these two groups did not differ significantly. The evidence indicated that postmature babies at birth must weigh, on the average, somewhat less than the maximum they attain before birth and that their intrauterine growth is limited by the functional capacities of the placenta.

The significance of postmaturity has long been a matter of controversy. Discussions are centered on what constitutes postmaturity, whether there is a postmaturity syndrome, and whether postmaturity is clinically significant in fetal and neonatal mortality. Our study was undertaken in an attempt to answer these questions. The concept of postmaturity as a well-defined entity has not been universally accepted. Various criteria have been suggested for determining whether an infant is postmature. The most commonly used one is the gestational age as calculated from the first day of the last menstrual period of the mother, according to the rule of Naegele. Gestational periods exceeding the average of 280 days by 7, 10, 14, 15, and 20 days have been regarded by various authors as indicating postmaturity.[1] The latter probably is the best indication, since this longer period may compensate for a late date of conception and for irregular and long menstrual periods. Other authors demand more complicated criteria for diagnosis of postmaturity, such as excessive weight and length.[2] For example, the Chicago Board of Health designates a postmature infant as one that weighs 4,250 gm. (9.5 lb.) or more at birth.[3]

From the Sarah Morris Hospital for Children, Michael Reese Hospital.

History of Syndrome

As early as 1902 Ballantyne[4] was of the opinion that anatomic indications of postmaturity could be seen in

the skin and its appendages, such as absence of lanugo and vernix caseosa, the presence of desquamation, and the absence of the normal red color of the skin. In the group studied by Taylor and others [5] of 37 babies whose skin, vernix caseosa, nails, and umbilical cord were stained yellow, 30% had gestation periods of 300 days or more. Ley [6] has noticed some relationship between dry, scaling skin and postmaturity. Clifford [1] believes that there is clinically a postmature syndrome and in 1954 made such a diagnosis in 37 newborn infants. He divided the syndrome into three stages. In the first stage he describes long, thin infants with dry, cracking, parchment-like skin; the second stage is more severe, with green staining of the skin and umbilical cord; in the third stage the staining is yellow instead of green. Many of the mothers of these babies did not have gestation periods over 300 days, but all periods were over 280 days.

It has been generally supposed that with prolongation of pregnancy there is an increase in fetal mortality. In 1941 Clayton [7] was among the first to confirm the impression that mortality is higher among postmature infants. Subsequently, other investigators [8] supported Clayton. In Clifford's [1] group of postmature infants 90% of the mortality occurred in infants born of women who had one, and only one, delivery in a 10-year period. In this group postmaturity ranked second only to prematurity as a cause of fetal and neonatal mortality. It should be noted that in Clifford's series of postmature infants born to multiparas there was no significant increase in mortality.

Patient Material and Methods of Study

Infants with gestational ages of 294 days and over were classified as postmature. Since the gestational ages as recorded on the neonatal charts are often only approximate, the maternal charts were studied to determine the correct gestational ages. Women who had irregular menstrual cycles were excluded. Maternal charts from Jan. 1 through Dec. 31, 1954, numbering 2,877, were reviewed. After the selection of maternal charts, the corresponding neonatal charts were then appraised and the following information obtained: race, sex, weight, length, physical appearance of the baby as described by the examining physician and nurse, morbidity, mortality, and postmortem findings. Two hundred fifty-two infants born during the same period were used as controls. Their neonatal charts were selected by random sampling. Infants with gestational ages below 259 days (premature infants) or above 294 days were excluded and replaced by selecting the next admission number. The approximate gestational ages on the neonatal charts were checked against the definitive ages in the maternal charts.

Results

Of 2,877 infants delivered there were 247 with gestational ages of 294 days or over, an incidence of 8.59%. Of these there were 132 babies with gestational ages of 300 days or over, an incidence of 4.59%. The average length of the 247 infants was 52.39 cm. (20.5 in.), with a range of from 45 to 58 cm. (18 to 23 in.). The average weight was 3,470 gm. (7.5 lb.), with a range of from 1,975 to 5,480 gm. (4.25 to 12 lb.). The average length of the control group was 52.42 cm. (20.5 in.), with a range of from 45 to 58 cm. (18 to 21 in.). Their average weight was 3,450 gm. (7.5 lb.), with a range of from 1,995 to 4,670 gm. (4.5 to 10.25 lb.). The distribution of the heights and weights of both groups is presented in figures 1 and 2. The two groups

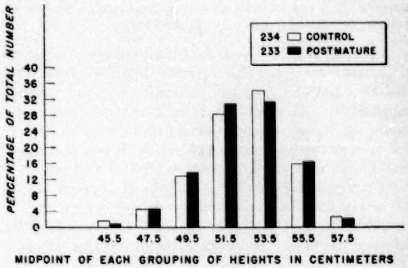


Fig. 1.—Distribution of heights of control and postmature infants.

were virtually identical. This implies that the control group is satisfactory with respect to these two variables. Approximately one-quarter of the postmature and control populations were Negro. The sexes were almost equally divided in both groups.

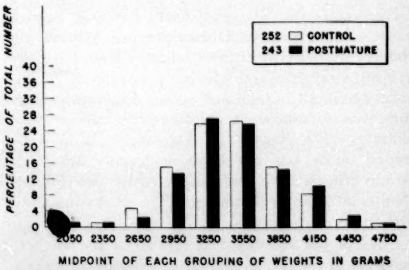


Fig. 2.—Distribution of weights of control and postmature infants.

Of the 247 postmature infants there were 11 (see table) who presented clinical findings consistent with the syndrome described by Clifford. None of these infants had jaundice due to hemolytic disease or other specific causes. In all but two, a gestational age of 40 weeks or less was recorded on the neonatal chart; however, the gestational ages on the corresponding maternal charts indicated 294 days or over, so that all of these babies were postmature. Five of the 11 were given a diagnosis of possible postmaturity at the time of birth. According to the descriptions recorded on the infants' charts, the remaining six presented good

evidence of the postmature syndrome. Since this is a retrospective study and there was no stress placed upon the examining physicians as to the significance of the postmaturity syndrome, the incidence of this syndrome in our series may tend to be low. Four of the 11 case histories are presented below.

Report of Cases

Case 1.—A Negro female baby had a gestational age of 307 days; however, 40 weeks was listed as the gestational age on the neonatal chart. She was 52 cm. (20.5 in.) in length and weighed 3,440 gm. (7.5 lb.). The infant was born covered with meconium, and there was meconium present in the amniotic fluid. She was in respiratory distress at birth. A tracheal catheter was used, and she improved. On arrival at the nursery, she was limp and cyanotic, and had slow, gasping respirations. The skin was very dry, cracked, and parchment-like, with poor turgor. The muscle tone was very poor. Breath sounds came through poorly over the right anterior and left posterior sides of the chest. The heart rate was 120 per minute. An extra digit was noted on the left hand. The impression of the examiner ot that time was of cerebral anoxia and atelectasis. The baby died 10 hours after birth. Postmortem examination revealed a good number of lanugo hairs, squamous cells, and eosinophilic fibrillar material in the alveoli. Many of the alveoli were collapsed. There was desquamation of the epithelial lining of many of the bronchi.

Data in Eleven Cases of Placental Dysfunction Syndrome

Case No.	Race	Sex	Age of Mother	Parity		Gestational Age of Infant, Days	Birth Weight, Gm.	Length, Cm.
				Gravida	Para			
1	N	F	27	5	3	307	3,440*	52
2	W	F	25	1	..	295	3,360	52
3	W	M	32	4	1	306	3,830	57
4	N	F	43	19	11	295	1,975	47
5	W	M	32	2	..	308	3,390	52
6	W	F	31	1	..	308	2,950	48
7	W	M	36	3	3	295	3,410	55
8	W	F	27	3	1	304	4,180	53
9	W	F	26	1	..	300	3,920	53
10	W	F	26	1	..	300	3,100	53
11	W	F	33	4	2	297	3,200	53
	Average		30.7			300.9	3,341	52.5

*Patient died.

Case 2.—A white female baby had a gestational age of 295 days. Thirty-seven weeks was listed as the gestational age on the neonatal chart. She was 52 cm. (20.5 in.) in length and weighed 3,360 gm. (7.5 lb.). The pertinent physical findings as listed by the examiner are as follows: 1. "The infant's skin is cracked and dry. 2. The muscle tissue is wasted. 3. She has an old-looking face." Despite the findings the infant survived.

Case 3.—A white male infant had a gestational age of 306 days. Forty weeks was listed as the gestational age on the neonatal chart. He was 57 cm. (22.75 in.) in length and weighed 3,830 gm. (8.5 lb.). A resident physician was called to see the child because of respiratory difficulty. The skin and vernix caseosa were stained yellow, and the cord was black. The infant recovered.

Case 4.—A Negro female infant had a gestational age of 295 days. Forty-two weeks was listed as the gestational age on the neonatal chart. The infant was 47 cm. (18.75 in.) long and weighed 1,975 gm. (4.25 lb.). The skin was dry and peeling. She was cyanotic at birth, had rapid respirations, and was hypotonic. Generalized rales were heard in both lungs. A tracheal catheter, alpha-lobeline, and a Freeman resuscitator were used. The baby improved and was discharged.

All 11 patients presented more than one of the clinical findings as described by Clifford; namely, dry, scaling, parchment-like skin; staining of the skin and vernix caseosa; and evidence of recent weight loss. Six of the 11 patients had respiratory difficulties. Of the 252 controls, there was only one infant who presented findings consistent with the syndrome. This infant had a gestational age of 280 days, length of 52 cm. (20.5 in.), and weight of 3,520 gm. (7.75 lb.). There is less than a 1% probability that the difference in the relative frequency of the syndrome in these two groups was due to chance alone. Among 11 babies with the syndrome, there was one neonatal death (case 1). Among the other 236 babies, there were 3 stillbirths and one neonatal death, in which autopsy revealed cerebral edema, congenital atelectasis, focal emphysema, and absence of the right leaf of the diaphragm. This makes a total perinatal mortality of five, or 2.02%, which is not high for infants of all gestational ages.[9] There were 132 babies with gestational ages of 300 days and over. Four of the five dead infants had gestational ages of over 300 days. The perinatal mortality rate in this group was 3.03%. The ages of the mothers of the five dead babies ranged from 26 to 37 years. Four of the five were multiparous; the other was a gravida 3, para 0.

There were no deaths in the control group. This is not statistically significant, since only neonatal charts were used initially in selecting a control group and stillborn children do not have neonatal charts. Three of the five postmature deaths were due to stillbirth. One of the two neonatal deaths occurred within several minutes after birth, and no neonatal chart was completed. The other was accounted for on the postmature neonatal chart. Postmortem findings revealed congenital atelectasis in two stillbirths and in one of the neonatal deaths. In the latter there was cerebral edema and absence of the right leaf of the diaphragm. Cerebral edema was also found in one of the stillborn children. One stillborn child had autolysis of the organs. The infant in case 1 had evidence of hyaline membrane disease with small areas of atelectasis. Of the total 2,877 patients, 2 were anencephalic. One of the anencephalic infants had a gestational age of 292 days, the other 267 days.

Comment

In our series the incidence of infants with gestational ages of 294 days or over was 8.59% and of those with gestational ages of 300 days and over 4.59%; this falls into the range of other investigators. It is unlikely that this incidence will change in the near future, since most obstetricians neither recognize nor accept the concept of postmaturity. Holmes [10] says that postmaturity is a "figment of the imagination." Postmaturity is minimized in standard obstetric textbooks,[11] and because of this most obstetricians in this country are not inclined to induce delivery, let alone perform cesarean section, in women with prolonged pregnancies. Obviously, these are the main procedures that will reduce the incidence of postmaturity.

The weights and lengths of our 247 postmature infants were approximately the same as those found in

infants of average gestational age. In Solth's [12] series of postmature infants there was no significant increase in length or weight. Solth stated that the growth curve of the fetus remains stationary after 300 days and that, after a child has achieved a certain state of development, postmaturity can no longer increase its weight or length. Experiments in both animals and humans suggest that, after term is reached, the placenta is no longer able to provide adequate nutrition to the fetus and that, if pregnancy is prolonged, the fetus may even be forced to live off of its own tissues.[13] Kamperman [13A] states that if a baby is postmature 20 days or more it begins to lose weight.

There is a diminished amount of vernix caseosa in postmature infants, and, if this lack is present in utero, the loss of this protective layer leads to maceration of the fetal skin with resultant drying and excessive peeling after the infant is born. The discoloration of the skin is caused by passage of meconium in utero and, most likely, is the result of fetal anoxia, which causes relaxation of the anal sphincter.[1]

Fetal anoxia as evidenced by fetal distress is more common in postmature infants than in full-term infants. As further proof of fetal anoxia in postmaturity, Walker [14] has shown that there is a significant decrease in the oxygen content in the umbilical vein by the 43rd week of pregnancy. At the 43rd week the fetus is just able to receive enough oxygen from the blood for its needs in a resting state and returns little or no oxygen to the placenta. Any stress or strain on the fetus, such as increased activity or infection of the mother, may lead to insufficient oxygen saturation of the blood supplying the fetal brain; this may be a principal factor in producing symptoms such as passage of meconium or postnatal dyspnea or in ultimately producing death.

That inadequate placental function is responsible for the deficient supply of oxygen to the postmature infant is highly probable. Flexner and associates [13a] have shown that human placental permeability declines after reaching its peak at 36 weeks. Furthermore, Barcroft and Young [13b] have found that, when pregnancies in rabbits are prolonged several days past term, the placenta rapidly becomes unable to transmit enough oxygen to support the cerebral circulation of the fetus and that often the fetus dies. Our study lends support to the concept of placental dysfunction. That inadequate placental function may be responsible for the syndrome is borne out not only by the physical appearance of our 11 babies but also by the fact that 6 of the 11 had clinical evidence of anoxia.

Five of the 11 infants had evidence of poor tissue turgor or subcutaneous tissue wasting. This could very well mean that at one time the fetuses weighed more than they did at birth; it also probably explains the reason why an infant in our study was premature by birth weight and postmature by gestational age (case 4). Of the 247 infants who were postmature according to gestational age, only 11 had evidence of the syndrome. This is important, because it demonstrates that most postmature babies as defined by gestational age do not have a characteristic syndrome. The syndrome has been seen in infants born prematurely and at the expected date of delivery.[15] Therefore, "placental dysfunction syndrome," as suggested by Clifford, is probably a better term than "postmaturity syndrome," since it may include infants of all gestational ages who present this clinical syndrome. As a result of our studies it is evident that the placental dysfunction syndrome occurs more frequently in postmature infants than in those of average gestational age.

Hyaline membrane disease is said to be more common in postmature infants than in newborn infants of average gestational age.[16] Only one of the two postmature children who died had lungs that showed histological findings suggestive of hyaline membrane disease (case 1). The most frequent pathological findings in postmature infants are confined to the lungs. These include aspiration of amniotic fluid and meconium, squamous cells and amorphous debris in the alveoli, and areas of atelectasis.[1] Congenital anomalies of the brain and spinal cord have been said to occur more frequently in postmature babies. The one most commonly associated with prolonged pregnancy is that of anencephalia.[17] Whether the delay in the onset of labor may be due to the lack of the normal stimulant of a presenting part in contact with the lower uterine segment is a moot question. The low incidence (2 of 2,877 deliveries) of anencephalia in our study makes it difficult for us to correlate the anomaly with postmaturity.

The mortality in our series was not significantly higher than in infants of average gestational age. This is not in agreement with the studies of others.[18] In our selected population of births following prolonged gestation all of the five perinatal deaths occurred in babies of mothers 26 years of age and over. Of the 247 mothers of postmature infants, 141 were from 26 to 33 years of age, whereas 106 ranged from 17 to 25 years of age. This is consistent with Von Rutte's [19] statement that postmaturity produces the greatest risks in babies of elderly mothers.

Summary and Conclusions

The incidence of postmaturity in our study, an overall percentage of 8.59 in infants 294 days and over and 4.59 in infants 300 days and over, is about the same as that found by other investigators and probably will not change significantly in the near future. Postmaturity does not signify a large baby. There is a definite placental dysfunction syndrome that occurs more often in postmature infants than in those of average gestational age. Because the syndrome is not confined exclusively to postmature infants, the term postmaturity syndrome should be discarded. Perinatal mortality does not appear to be significantly higher in postmature babies than in full-term babies.

29th Street and Ellis Avenue (16) (Dr. Kunstadter).

References

1. Clifford, S. H.: Postmaturity—with Placental Dysfunction: Clinical Syndrome and Pathologic Findings, J. Pediat. **44:** 1-13 (Jan.) 1954.
2. Kortenoever, M. E.: Pathology of Pregnancy: Pregnancy of Long Duration and Postmature Infant, Obst. & Gynec. Surv. **5:** 812-813 (Dec.) 1950.
3. Bundesen, H. N., and others: Progress in Prevention of Needless Neonatal Deaths, Chicago, Chicago Department of Health, 1952, p. 39.
4. Ballantyne, J. W.: Problem of Postmature Infant, J. Obst. & Gynaec. Brit. Emp. **2:** 521-524, 1902.
5. Taylor, W. C.; James, J. A., and Henderson, J. L.: Significance of Yellow Vernix in Newborn, Arch. Dis. Childhood **29:** 442-444 (Oct.) 1952.
6. Ley, G. D.: Some Aspects of Prolonged Gestation, M. J. Australia **2:** 749-752 (Nov. 14) 1953.
7. Clayton, S. G.: Foetal Mortality in Postmaturity, J. Obst. & Gynaec. Brit. Emp. **48:** 450-460 (Aug.) 1941.
8. Footnotes 1 and 2.
9. Gold, E. M.: Perinatal Mortality, J. A. M. A. **159:** 244-247 (Sept. 24) 1955.
10. Holmes, R. W., in discussion on Calkins, L. A.: Postmaturity, Am. J. Obst. & Gynec. **56:** 171 (July) 1948.
11. Eastman, N. J.; Williams Obstetrics, ed. 10, New York, Appleton-Century-Crofts, Inc., 1950, p. 199.
12. Solth, K.: Die intrauterine Kindsentwicklung bei verlängerter Tragzeit, Geburtsh. u. Frauench. **7:** 134-146 (Dec.) 1947.
13. (*a*) Flexner, L. B., and others: Permeability of Human Placenta to Sodium in Normal and Abnormal Pregnancies and Supply of Sodium to Human Fetus as Determined with Radioactive Sodium, Am. J. Obst. & Gynec. **55:** 469-480 (March) 1948. (*b*) Barcroft, J., and Young, I. M.: Internal Oxygen Environment of Brains of Post-Mature Rabbit Embryos, J. Exper. Biol. **21:** 70-76 (Jan.) 1945.
13.A. Kamperman, G., in discussion on Calkins, L. A.: Postmaturity, Am. J. Obst. & Gynec. **56:** 170 (July) 1948.
14. Walker, J.: Foetal Anoxia (Blair-Bell Memorial Lecture), J. Obst. & Gynaec. Brit. Emp. **61:** 162-180 (April) 1954.
15. Platou, R. V.: Personal communication to the authors.
16. Smith, C. A.: Valley of Shadow of Birth, A.M.A. Am. J. Dis. Child. **82:** 171-201 (Aug.) 1951.
17. Malpas, P.: Postmaturity and Malformation of Foetus, J. Obst. & Gynaec. Brit. Emp. **40:** 1046-1053 (Oct.) 1933.
18. Footnotes 1 and 7.
19. Von Rutte, U.: Der Fruchttod bei verlängerten Schwangerschaften, Schweiz. med. Wchnschr. **79:** 1123-1126 (Nov. 26) 1949.

ETIOLOGY AND MECHANISM OF HARRISON'S GROOVES

Henry A. Brodkin, M. D., Newark, N.J.

• *The horizontal grooves (Harrison's) consisting of the drepressions of the sixth and seventh costal cartilages are always at the site of the attachment of the anterior portion of the diaphragm. They are ascribed either to rickets or to increased negative pressure due to chronic respiratory difficulty in infancy. As a result of studies of the action of the diaphragm and its relation to the development of the normal thorax as well as to the development of the other anterior chest wall deformities funnel chest and pigeon breast, evidence is given to support the theory that all three deformities are produced by abnormal contractions of the diaphragm during infancy. Normal (balanced) diaphragmatic contractions produce no inspiratory retraction deformities of the anterior chest wall in spite of the fact that the anterior portion of the diaphragm is the smallest and weakest portion. Unbalanced diaphragmatic contractions will produce an inspiratory retraction of some portion of the chondrosternal area if the anterior portion of the diaphragm is congenitally weaker or deficient or if abnormally strong diaphragmatic contractions are induced by chronic dyspneic conditions when the anterior chest wall is still soft and yielding. A severe unilateral Harrison's groove was corrected surgically by freeing the six and seventh costal cartilages from their diaphragmatic attachment and suturing them in their new relaxed positions.*

Harrison's grooves were first described approximately 120 years ago, but their etiology and mechanism have remained controversial and unsettled. An editorial [1] in the *British Medical Journal*, in giving strong support to an article on Harrison's grooves by Naish and Wallis [2] stated, "Much confusion regarding this point exists to the present day and they are certainly not produced at the attachment of the diaphragm to the ribs as many textbooks continue to assert." Naish and Wallis take issue particularly with Holt and McIntosh,[3] Nelson,[4] and Paterson and Moncrieff,[5] who state that Harrison's grooves are produced by an inward pull of the diaphragm at its costal attachments. American authors [6] and Collis and Kawerau [7] treat the condition as a manifestation of rickets, whereas English authors [8] believe they are produced by an increase in the negative intrapleural pressure. Furthermore, there is no agreement among the English authors as to why Harrison's grooves are produced in their particular location. The *British Medical Journal* editorial stated also, "The exact mechanism of the development of these grooves remains in some doubt, though the presumption is that it is associated with conditions producing increased intrathoracic traction." I will present a theory that may satisfactorily explain the "exact mechanism" of the development of Harrison's grooves.

For a proper definition of Harrison's grooves one must distinguish between those in infants and those in children and adults. In infants, they are horizontal mobile concavities created by and synchronous with the retraction of the diaphragmatic attachment at the sixth costal cartilage during normal inspiration. Harrison's grooves are sometimes present at birth, although they are frequently overlooked at that time. As one watches the quiet breathing of an infant with Harrison's grooves and observes the creation of these horizontal concavities during inspiration and places the tips of his fingers in the depth of the concavity along the sixth costal cartilage, one cannot escape the conclusion that the diaphragm is the mechanical factor that produces Harrison's grooves. This conclusion was proved to my satisfaction by paralyzing the hemidiaphragm after the injection of 1% procaine hydrochloride into the phrenic nerve in an infant's neck and observing the cessation of this inspiratory retraction. However, if one looks at the fixed Harrison's grooves in a child, one may speculate on the possible factors that produced them. In children, as the thorax elongates, flattens, and becomes more firm, the grooves become immobile during respiration and appear much lower; but the deepest part of the concavity remains over the retracted sixth costal cartilage. There is normally a slight horizontal concavity in this part of the chest in normal children and adults. Naish and Wallis [2]

From Newark Beth Israel Hospital.

found in a group of 500 normal school children that 45% had detectable grooves and that 7% of this group had grooves with depths of 3/16 in. or more at the deepest point. Harrison's grooves vary in depth, are usually bilateral but may be unilateral, and may be

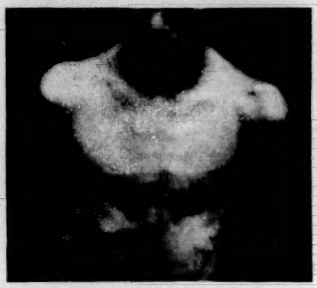


Fig. 1.—Seven-year-old boy with well-developed Harrison's grooves, which were noted at birth. The child has been free of rickets. Note that the grooves are deepest at the sixth costal cartilages and the attachment of the anterior segment of the diaphragm.

seen in combination with funnel chest and pigeon breast. The anterior flare of the lower ribs due to conditions resulting from abdominal distention is not considered typical Harrison's grooves.

Fig. 2.—Normal 2-year-old infant with typical Harrison's grooves, which still show some inspiratory retraction at the attachments of the anterior muscular segments of the diaphragm to the sixth costal cartilage. Mother has a congenital funnel chest with congenital absence of left breast. Child had no evidence of rickets.

Rickets undoubtedly influences the bone and cartilage development of the chondro-costal-sternal area and as a result will produce and aggravate abnormalities of the anterior chest. E. A. Park [1] stated, "Thirty years ago the Harriet Lane Pavilion at Johns Hopkins Hospital was literally filled with children who had rickets, together with Harrison's grooves and other chest and bone deformities; whereas today these rachitic deformities have almost disappeared, yet Harrison's grooves are still quite common and very often occur in otherwise perfectly normal children." Inasmuch as these observations were made on apparently nonrachitic infants and children, rickets as a primary factor will not be discussed herein, although I agree with the English writers who state that Harrison's groove is valueless as a sign of early rickets.

Naish and Wallis,[2] after a study of several groups of school children between the ages of 5 and 12 years, came to the conclusion that the most important factor in the production of Harrison's grooves is "deficient expansion of the lungs." Although they found an incidence of 7% of distinct Harrison's grooves in 500 normal school children, they provided no reason for this occurrence. It appears that they based their conclusion on the fact that Harrison's grooves were more frequent in children who had had rickets, chronic bronchial asthma, severe congenital heart lesions, or repeated attacks of pneumonia. The report offered no apparent explanation as to why the majority of the children with these conditions had normal chests. It would have been extremely important in this study to know when the Harrison's grooves had been first noticed in these children. It is unfortunate that these investigators did not study a group of children from birth and observe those with Harrison's grooves as they developed into childhood.

The currently accepted etiological factors are questioned because of the following facts. Today, the majority of children with Harrison's grooves are normal healthy children whose medical histories furnish no clue as to the etiology. Moreover, the majority of normal children who have had conditions and diseases that are presumed to be responsible for causing Harrison's grooves have perfectly normal chests. Furthermore, if two large separate groups, one of infants and the other of children, are examined for Harrison's grooves, the incidence will be approximately the same, since the grooves are most often first noted during infancy. The medical histories of the children with Harrison's grooves will disclose a certain percentage of the group to have had rickets and conditions with chronic dyspnea that will be regarded as the cause. Practically all of the medical histories of the infants with Harrison's grooves will be negative for dyspneic conditions because the infants will not have lived long enough to develop such conditions. Therefore, these illnesses and conditions are very often coincidental to the development of the grooves but contributory to their severity. Thus, we must seek an etiology and mechanism that will apply equally to both infants and children. There is one condition that will produce an inspiratory retraction of the sixth costal cartilage, which is the most yielding part of the anterior chest wall, namely, an unbalanced contraction of the diaphragm, which may be produced by severe dyspnea or deficiency of the anterior segment of the diaphragm. I will discuss, first, the mechanical forces that produce the complex but normal balanced contractions of the diaphragm and, second, the etiology and mechanism that produce the unbalanced diaphragmatic contractions that create Harrison's grooves.

It has been interesting to note the change concerning the etiology for funnel chest from the formerly current beliefs to the recent suggestions [9a] of a "hypertrophied retrosternal ligament" and a "short central tendon of the diaphragm" as the cause. Of these suggestions, I question the existence of the former and the role of the latter. In more than 50 operations for the relief of pectus excavatum, I have never been satisfied with what has been described as a "hypertrophied retrosternal ligament." In addition, both structures, being fibrous, are consequently passive and therefore incapable by themselves of moving or affecting the anterior chest wall. In previous reports,[10] I have suggested as the cause for the funnel chest unbalanced diaphragmatic contractions resulting from a congenital weakness or deficiency of the anterior segment of the diaphragm. This principle also applies to Harrison's grooves.

Diaphragm

The key to the understanding of the formation of the congenital anterior chest wall deformities is an appreciation of the forces involved in the complex normal contraction of the diaphragm and the changes in those forces that produce an abnormal contraction. The diaphragm is a dome-shaped musculotendinous structure formed by a fusion of four embryonic segments. The muscular portion of the normally developed diaphragm consists of radiating muscle fibers whose origin is along the edge of the thoracic outlet. These terminate in long tendinous fibers that are inserted, bound, and fused together into the trefoil fibrous membrane. Each hemidiaphragm consists of three unequal segments. The anterior, the smallest and weakest, is almost joined as one segment with that of the other hemidiaphragm and arises at the gladiolus-xiphoid junction and sixth costal cartilages. The lateral segments are longer and stronger and arise along the lower margins of the 7th to the 11th ribs. The posterior segments, united as one, are the longest and strongest and arise along the 12th ribs and are joined together by the crura from the second and third lumbar vertebrae. In the normal infant whose thorax is practically inert, the domes of the diaphragm are comparatively flat and occupy a relatively high position and the costophrenic sinuses are shallow laterally and posteriorly and absent anteriorly.[11] Since there is little slack in the diaphragm anteriorly during expiration, any strong diaphragmatic contraction will make itself felt at that point first. In the longer and flatter thorax of children, the domes of the diaphragm are lengthened and rounded and the costophrenic sinuses are deeper.

During inspiration, the circumferential musculature of the diaphragm contracts radially from a central hub and the central trefoil tendinous portion toward its origin at the periphery of the thoracic outlet. As the radiating muscle fibers shorten and straighten, the costophrenic sinuses widen and each hemidiaphragm is drawn downward and taut. Each muscle bundle exerts a force or pull that is counterbalanced by an equal force or pull exerted by a muscle bundle that is radially opposite it across the central tendinous portion (fig. 3). This is contrary to current belief and to the descriptions in anatomy and physiology books, which state that the diaphragm as a whole descends in a slow piston-like motion. The central tendinous portion of the diaphragm that is fused with the fibrous pericardium is comparatively fixed and is held suspended from the thoracic inlet (Sibson's fascia) by the fibrous pericardium, which extends up and fuses with the deep fascia of the neck. This point is further fixed by the pulmonary ligaments and indirectly by structures at the roots of the lungs, the phrenic nerves, the mediastinal pleurae, and the great vessels extending up into the neck and arms. The relative immobility of this central point in the diaphragm becomes apparent when the action of the diaphragm is observed under the fluoroscope in patients with pneumoperitoneum. Normally, this is obscured by fusion of the cardiac and liver shadows, and the motion of this portion of the diaphragm has been assumed.

During the first year of life, the diaphragm need descend only a fraction of a centimeter in order to draw into the infant's lungs the average amount of

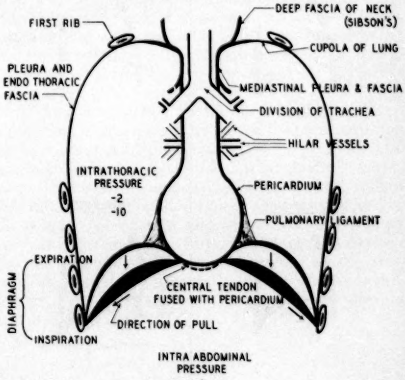


Fig. 3.—Schematic demonstration of how central portion of the membranous diaphragm that is fused with the inferior surface of the pericardium and the inferior pulmonary ligaments is relatively fixed and does not descend in a piston-like action.

tidal air required during normal inspiration. (This is roughly determined by taking the average circumference of the chest, which according to Kornfeld [12] is 31 cm. at birth and 46 cm. at the age of one year, and obtaining the area of the diaphragm. The total area of the diaphragm is divided into the average amount of tidal air, which is 27 cc. at birth and 48 cc. at one year.[13]) The mechanism of the descent of the normal diaphragm may be graphically demonstrated if we look at one plane of the thorax as seen in the lateral view, although it applies to all planes along the entire circumference (fig. 4). In this way we see that the force Z, by which the diaphragm descends, is the resultant of two unparallel forces,[14] namely, X, the force of the ventral pull of the anterior segment, and Y, the force of the dorsal pull of the dorsal segment. Force Z, the resultant force of forces X and Y, by which the diaphragm descends, overcomes and exceeds the sum of the opposing positive intra-abdominal pressure and

the upward negative intrapleural pressure. Z is therefore a force that must overcome a resistance equivalent to 18 cm. H_2O pressure at the end of normal inspiration (since the intra-abdominal pressure is +3 and +8 and the intrapleural pressure is −2 and −10). Force Z is balanced and divided between the forces X and Y. Thus, during the normal inspiration of the infant, each muscular segment is capable of meeting the normal demands of inspiration by a balanced diaphragmatic contraction.

In the presence of dyspnea or respiratory obstructive conditions, the diaphragm is forced into stronger contractions to the limit of each muscular segment's capability. If, however, greater and greater demands are made on the diaphragm for stronger and stronger contractions, the weak anterior segment will reach the limits of its power first. Beyond this point it will be overpowered by the stronger lateral and posterior segments, as in a tug of war, and will be pulled back during abnormally strong diaphragmatic contractions on deep inspiration. Thus, an unbalanced contraction of the diaphragm occurs in which the anterior segment with its anterior attachment is pulled back and an inspiratory retraction of the sixth costal cartilages, or Harrison's groove, occurs. This can be illustrated if the mouth and nose of a normal infant are momentarily closed to block the ingress of air. It is frequently seen during the early inspiratory efforts of the infant when its tracheobronchial tree is still filled with secretions and the diaphragmatic contractions are violent, so that deep chondrosternal retractions occur. These disappear as soon as the infant's tracheobronchial tree is cleared and there is no further obstruction in the inflow of air into the lungs. These retractions are commonly seen for short periods in premature infants, who have greater difficulty with respiration and cannot easily clear the bronchial secretions. A striking example illustrating this phenomenon is described by Potter [15] in a case in which the newborn infant breathed normally for the first two hours but gradually became progressively dyspneic, so that with each inspiration a progressively deeper funnel chest was produced until asphyxia took place (an infant with resorption atelectasis).

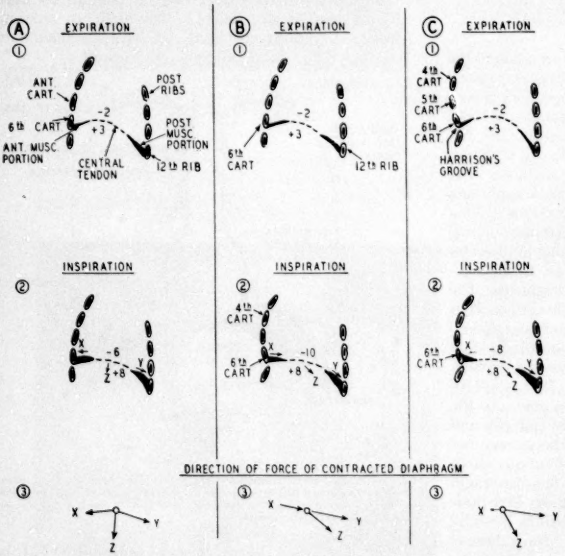


Fig. 4.—Lateral views of the thoracic wall and diaphragm showing the forces and directional pull of the anterior and posterior muscle segments in *A*, normal infant and in *B* and *C*, infant and child with Harrison's grooves. *A*, 1, 2, and 3 show that a normal balanced diaphragmatic contraction in a normal infant produces no retraction of the sixth costal cartilage, the point of attachment of the anterior segment. *B*, 1, 2, and 3 demonstrate the retraction of the sixth costal cartilage producing Harrison's grooves in an infant during inspiration because of an unbalanced diaphragmatic contraction due to a weak anterior muscular segment or increased intrapleural pressure. *C*, 1, 2, and 3 demonstrate the contraction of a diaphragm in children in whom the Harrison's grooves have become fixed. O, origin of unparallel forces; X, direction of anterior force of contracted anterior portion; Y, direction of posterior force of contracted posterior portion; Z, direction of resultant force, which makes diaphragm descend.

Combined Deformities

Harrison's grooves occur in combination with the two other anterior chest wall deformities known as funnel chest and pigeon breast. In funnel chest alone, the sternal or medial portion of the anterior segments of the diaphragm is deficient. When Harrison's grooves are present alone the costal or lateral portion of the anterior segment that is attached to the sixth costal cartilage is deficient. When they occur with funnel chest, Harrison's grooves are almost completely overshadowed, because the retraction of the chondrosternal area is more diffuse and the grooves merge into the rest of the depression. In the pigeon breast deformity, which is usually accompanied by Harrison's grooves, the grooves are more distinct. Pigeon breast has always been regarded as a manifestation of rickets. Inasmuch as Harrison's grooves are so frequently seen in combination with pigeon breast, they, too, have been ascribed to rickets. I have previously attributed pigeon breast to abnormal unbalanced diaphragmatic contractions and described an abnormal diaphragm in a patient with this combination.[10]

Determination of Etiology

In a premature or a newborn infant, the presence of Harrison's grooves may indicate mechanical interference with inspiration; therefore, immediate measures must be taken to free the tracheobronchial tree of secretions. In the majority of premature infants, the grooves will disappear when the infant attains full development and strength. In some newborn infants, the grooves will disappear after a few days, when the lungs are cleared of excessive secretions. In a few infants I have seen, the grooves were present for several weeks after birth and then gradually disappeared. This was probably due to the fact

that the anterior segment of the diaphragm was too weak at birth but gradually increased in strength until it could overcome the posterior pull of the other segments. In some otherwise normal infants, Harrison's grooves appear at birth and continue through infancy and childhood into adult life. In these cases, the most probable cause is a congenital weakness or deficiency of the anterior segment of the diaphragm. On the other hand, if, during the first few years of life, a child with a normal thorax begins to have severe prolonged dyspnea, Harrison's grooves will appear and, if they continue long in childhood, will become permanent. Here rickets may play a contributing part in increasing the severity of the grooves, since the cartilages are more yielding. This explains the discrepancy of finding Harrison's grooves in some children who have had frequent attacks of asthma and pneumonia during infancy while the majority of the children with the same illnesses or conditions have normal chests.

When dyspnea is severe enough, the unusually strong diaphragmatic contractions not only increase the negative intrathoracic pressure but also retract the attachment of the anterior segment of the diaphragm to the sixth costal cartilage. Therefore, the etiology for the grooves in such children actually is the unbalanced diaphragmatic contractions rather than the illnesses or the higher negative pressure. Thus, Harrison's grooves are not due to any "sucking-in action" of high negative intrathoracic pressure or a "pushing in" due to the atmospheric pressure, as many have suggested. Dyspnea is less apt to produce these grooves during childhood after the thorax has become flat and firm. Therefore, if a careful history is determined of a child with Harrison's grooves, particularly as to the time the grooves were first noticed, a more accurate etiology will be obtained. Thus, if the grooves have been present since birth, the etiology is that of unbalanced diaphragmatic contractions due to a deficient or weak anterior segment of the diaphragm. If the grooves appeared later in infancy and severe prolonged dyspnea was present, then the etiology is unbalanced diaphragmatic contractions resulting from the strong diaphragmatic contraction necessary to overcome the greater negative intrathoracic pressure.

Report of a Case

A white 20-month-old female was admitted to St. Michael's Hospital and was referred to me for the correction of a severe unilateral Harrison's groove on the right side. The medical history was entirely negative except that her grandfather had a typical pigeon breast. A horizontal incision was made over the right sixth costal cartilage in the deepest part of the groove. The sixth costal cartilage was freed, and the soft structures underneath were seen to retract dorsally with each inspiratory contraction of the diaphragm. This, by feeling, could be ascertained to be caused by the part of the diaphragm that was attached at this point. The seventh costal cartilage was also cut free and, when both these cartilages were incised close to the sternum, they sprang free, rose to the cartilage above, and extended beyond the right sternal border. About 1 cm. of the ends of the sixth and seventh cartilages was removed, and the cartilages were sutured with wire in their new relaxed position. The excess pieces of cartilage were diced and placed beneath the sixth cartilage in the retracted space. After the wound was closed, there was no longer any inspiratory retraction and the contour of the right chest appeared normal.

I do not propose surgery for the correction of bilateral Harrison's grooves. However, in an infant with a distinct unilateral Harrison's groove creating an obvious deformity, surgical treatment as described above will produce a satisfactory cosmetic result.

Summary and Conclusions

The most recent concepts concerning the etiology of Harrison's grooves are controversial, leaving the subject unsettled. I have attempted to reconcile some of the anatomic and physiological factors that apply to the mechanism that produces Harrison's grooves. The three anterior chest wall deformities, funnel chest, pigeon breast, and Harrison's grooves, are due to unbalanced diaphragmatic contractions produced during infancy by a congenital abnormal development of the anterior segment of the diaphragm. The normally developed diaphragm will produce a balanced contraction without retracting any portion of the thoracic wall, whereas weakness or underdevelopment of a portion or of the whole of the anterior segment of the diaphragm will result in an unbalancing of these forces and a retraction of the diaphragm's attachment to the anterior chest wall by the stronger posterior and lateral segments. Specifically, in the case of Harrison's grooves, the pull is on that portion of the anterior segment that is attached to the sixth costal cartilage. Conditions characterized by severe dyspnea requiring stronger, deeper diaphragmatic contractions may also produce similar unbalanced diaphragmatic contractions. If this occurs when the anterior chest wall is still soft and yielding, deformities may be produced or the severity of existing ones increased. This theory will not only remove the strong feeling of guilt mothers develop because they blame themselves for the presence of these deformities but also absolve the pediatrician or family doctor for having failed to prevent and treat this deformity.

365 Osborne Terrace.

Dr. E. A. Park of Johns Hopkins Hospital gave advice and counsel in this study.

References

1. Fresh Thoughts on Harrison's Grooves, editorial, Brit. M. J. **1**: 553, 1948.
2. Naish, J. M., and Wallis, H. R. E.: Significance of Harrison's Grooves, Brit. M. J. **1**: 541, 1948.
3. Holt, L. E.: Holt Pediatrics, ed. 12, edited by L. E. Holt Jr. and R. McIntosh, New York, Appleton-Century-Crofts, Inc., 1953.
4. Textbook of Pediatrics, edited by W. E. Nelson, ed. 6, Philadelphia, W. B. Saunders Company, 1954.
5. Diseases of Children, edited by D. Paterson and A. Moncrieff, ed. 4, Baltimore, Williams & Wilkins Company, 1949, vol. 1.
6. Green, M., and Richmond, J. B.: Pediatric Diagnosis, Philadelphia, W. B. Saunders Company, 1954. Footnotes 3 and 4.
7. Fanconi, G., and Wallgren, A. J.: Textbook of Paediatrics, edited by W. R. F. Collis and E. Kawerau, New York, Grune & Stratton, Inc., 1954, p. 209.
8. Parsons, L. G., and Barling, S. G.: Diseases of Infancy and Childhood, ed. 2, New York, Oxford University Press, 1954. Footnotes 1, 2, and 5.
9. Park, E. A.: Personal communication to the author.
9a. Brown, A. L.: Pectus Excavatum (Funnel Chest) Anatomic Basis: Surgical Treatment of Incipient Stage in Infancy: and Correction of Deformity in Fully Developed Stage, J. Thoracic Surg. **9**: 164, 1939.
10. Brodkin, H. A.: Congenital Chondrosternal Prominence (Pigeon Breast): A New Interpretation, Pediatrics **3**: 286, 1949; Congenital Chondrosternal Depression (Funnel Chest): Its Treatment by Phrenosternolysis and Chondrosternoplasty, Dis. Chest **19**: 288, 1951; Congenital Anterior Chest Wall Deformities of Diaphragmatic Origin, ibid. **24**: 259, 1953.
11. Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology, ed. 2, Chicago, the Year Book Publishers, Inc., 1950.
12. Kornfeld, W.: Chest Development in Early Childhood, J. Pediat. **42**: 715, 1953.
13. Smith, C. A.: The Physiology of the New Born Infant, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1951.
14. Brodkin, R. H.: Personal communication to the author.
15. Potter, E. L.: Pathology of the Fetus and the New Born, Chicago, the Year Book Publishers, Inc., 1952.

CERVICAL SPONDYLOSIS AND COMPRESSION OF THE SPINAL CORD

Jackson Braham, M.C., M.D., M.R.C.P.
and
Eugene E. Herzberger, M.D., F.I.C.S., Tel Aviv, Israel

• *Indentation of the cervical part of the spinal cord by protrusion of intervertebral disks and by osteophytic lipping produces varied neurological symptoms directly by mechanical injury and indirectly by effects on the movement of blood and cerebrospinal fluid. Diagnosis depends on cerebrospinal fluid manometry and myelography, for the symptoms may have more than one cause.*

In one case, the extensive paralyses in the patient were found to result from amyotrophic lateral sclerosis in addition to osteophytes that had caused marked narrowing of the disk space at the fourth and fifth cervical levels. In a second case, gross spondylotic changes in the cervical region coexisted with a sarcoma that was blocking the canal completely in the thoracic region.

Laminectomy, with section of the dentate ligament, was done in six cases of chronic cord compression by cervical spondylosis. No improvement resulted in one case, and in two the results were hard to assess. But in three there was partial success, and two of these patients were relieved of symptoms and enabled to return to their occupations. This experience indicated that surgical treatment should be reserved for the patient in whom the symptoms are recent and rapidly progressing.

In recent years increasing attention has been paid to the role played by spondylosis in the production of cervical cord syndromes. Although as yet little or no mention is made of this subject in standard medical or neurological textbooks, a number of papers have emphasized its importance and frequency, particularly as a cause of disability in the older age groups.

Because of the ubiquity of cervical spondylosis in the general population and, in particular, among older people, there is an understandable reluctance to attribute neurological disturbances to this finding; however, as has been shown by Pallis and others [1] during an independent assessment of the radiological and neurological status in a group of elderly people, the connection is by no means fortuitous. It may well be, as these authors contend, that it is necessary to revise opinions about the "physiological" nature of various neurological findings in the senescent population. With the greater interest in this diagnostic possibility, certain general views have tended to crystallize with regard to problems of etiology, diagnosis, and treatment. These have been reviewed recently by Brain [2] on the basis of previous detailed communications,[3] and we, in this paper, wish to present some of these aspects as they have been met with in everyday neurological and neurosurgical practice. We are concerned here with cervical spondylosis as a cause of chronic cord compression and not of root pains only.

Pathological Mechanism

Gross indentation of the cervical cord by intervertebral disk protrusion and osteophytic lipping with local degeneration of gray and white matter has been described in postmortem studies by Bedford and others.[4] These findings probably represent the end-result in an extreme case, and in the more usual situation of the ambulant patient with moderate signs and symptoms it seems unlikely that a permanent state of severe cord compression exists.

We have been constantly impressed by the spinal manometric readings in our patients, where observations of pressure fluctuations have confirmed the findings, limited to cases of spondylotic compression, reported by Kaplan and Kennedy.[5] With the head bent forward, a free rise and fall is seen on jugular compression and release, whereas in moderate or especially in full retroflexion of the neck, partial or complete manometric block is observed. Direct visual confirmation of this phenomenon has been frequently obtainable on myelography, when the column of oil has been seen to be held up or deformed during retroflexion, a free passage being obtained on return of the neck to the normal or flexed position. This evidence clearly supports the contention that recurrent partial compression of the cord during the many opportunities presented by neck extension movements during everyday life represents the probable pathological mechanism responsible. The compression possibly operates via interference with circulation in the anterior spinal artery, and hence there is recurrent ischemia in the area irrigated by this vessel.

Again, one frequently encounters the acute cervical cord syndrome resulting from trauma in patients with previously asymptomatic cervical spondylosis. This syndrome was referred to by Brain [3] and emphasized with numerous examples by Symonds.[6] The type of trauma is often a fall on the face, and the acute onset, believed to be due to momentary crushing of the cord by osteophytic ridges during the concomitant forcible hyperextension of the neck, may be considered as representing a catastrophic shortening in time of the slow evolution referred to above.

Diagnosis

The patients' complaints are generally referred in a quite variable manner to disturbances of function in the limbs. Weakness of one or both legs, difficulty in climbing steps, stiffness, and a dragging gait have usually been present for months or years, and the patient is unable to recall the precise time of onset of his symptoms. Diffuse weakness in one or both upper limbs, with clumsiness in execution of fine movements, may be the presenting feature, and paresthesias are often complained of. Occasionally, disturbances re-

From the departments of neurology (Dr. Braham) and neurosurgery (Dr. Herzberger), Tel-Hashomer Government Hospital.

lated solely to an arm and leg on the same side may awaken suspicions of a hemiparesis of central origin. In some, progressive weakness culminating in severe paraplegia characterizes the picture, although relentless deterioration is not inevitable and stationary periods, or even episodes, of improvement may be reported, especially when there have been opportunities for rest in bed.

The physical signs are no less variable from case to case. In general, evidence of lesions of upper motor neurons supplying the lower limbs dominates the scene, and these changes are often bilateral, even when the patient's complaints are directed to one side of the body only. In the upper limbs, anomalies of the reflexes vary according to the site of the compression; inequality of briskness between the two sides in the presence of bilateral pyramidal signs in the lower limbs constitutes, when present, valuable evidence of a local cervical lesion. Sensory changes are even less constant, both in incidence and in variety. Diminished appreciation of pinprick in the lower half of the body may reach a level many segments below that of the compression. As the condition progresses, so may a gradual rise in this level be evident. Vibration sense in the toes is more commonly diminished than is superficial sensation. Detailed analysis of the subjective and objective sensory and motor patterns is available.[3]

Cerebrospinal fluid manometry has been referred to already, and, whenever performed with the flexion-extension technique described, it has invariably given confirmatory information. The fluid itself has shown no deviation from normal values, except for an occasional moderate rise in the protein content not exceeding 65 mg. per 100 cc. in our series. Myelography has been used to supplement or corroborate changes observed on plain films for accurate localization and for exclusion of other disorders. With a hyperextension technique,[7] no difficulty was experienced in concentrating the oil column in the cervical canal. Convincing evidence of local pressure by spondylotic ridges is thus obtained and most readily visualized in lateral films taken with the patient prone.

Differential Diagnosis

Radiological evidence of cervical spondylosis is very frequent in adults. Many of these people, perhaps the great majority, are free of complaints related to the nervous system, although perhaps objective changes are less rare than may be supposed.[1] It follows that great care must be exercised in attributing neurological signs and symptoms to this cause, even when it may seem anatomically appropriate.

From the review of the varied clinical picture that may result from cervical spondylosis as outlined above, it is clear that this disorder may easily be confused with disseminated sclerosis or subacute combined degeneration of the cord and, when sensory findings are absent, with amyotrophic lateral sclerosis, quite apart from other causes of cord compression, such as new growth. This confusion may operate as it were in both directions, as pointed out by Brain.[3] Thus spondylosis may be unrecognized as being the real cause of cord syndromes; it may be recognized and improperly invoked as the cause of disorders that are, in fact, degenerative; it may coexist with degenerative disorders and contribute in variable measure to the over-all clinical picture. The following representative case histories are illustrative of the diagnostic pitfalls inherent in such an ambiguous situation.

Case 1—Cervical Spondylosis Complicating Amyotrophic Lateral Sclerosis.—A 55-year-old man gave a history of weakness in the limbs of four years' duration. Beginning in the left hand, it had spread to the right side, and later to the legs, so that on admission he was completely bedridden and helpless. Gross atrophy of the small hand muscles was seen on both sides, with a lesser degree of wasting but considerable weakness of the more proximal muscles of the upper limbs. There was spasticity of the lower limbs, with extensor plantar responses. The deep reflexes in all four limbs were exaggerated, but there were no sensory changes. Fasciculation was widespread. Anterior and posterior osteophytes were seen on x-ray examination at C-4 to C-5, with marked narrowing of the disk space. Myelography revealed gross identation of the oil column at this level.

On further observation of this patient in the ward, a certain thickness of speech was discovered to be of fairly recent onset, according to his relatives. A very brisk jaw reflex was elicited, and there was gross fibrillation of the tongue; an opportunity to witness outbursts of uncontrollable laughter and weeping made certain that, whatever role was played in the total clinical picture by undoubted cervical cord compression, the patient certainly suffered also from amyotrophic lateral sclerosis.

Case 2—Cervical Spondylosis Complicating Compression of Thoracic Cord by Tumor.—A 52-year-old woman complained of increasing difficulty in walking for the previous six months, hitherto attributed to diffuse osteoarthritis. Examination revealed marked inequality of the biceps reflexes (those on the right being greater than those on the left) and increased tone in the lower limbs, with bilateral extensor plantar responses. Superficial sensation, vibration sense and position sense were somewhat impaired in the lower limbs, without any clear upper level. These findings were considered to be indicative of a mid-cervical lesion, and, indeed, gross spondylotic changes at C-4 to C-6 were appropriately evident radiologically; however, on lumbar puncture, there was complete manometric block in all positions of the head, and the fluid contained 100 mg. of protein per 100 cc., findings rather more decisively pathological than had been within our experience in spondylosis cases. Myelography resulted in the unexpected discovery of complete block at T-9, at which level compression by tumor (sarcoma) was disclosed at a subsequent operation. In this patient, the physical findings could very well have been explained on the basis of the undoubted cervical spondylosis, with unfortunate results if confirmatory myelography had not been performed. On the basis of this experience, which was repeated in another patient with high cervical compression due to a meningioma, again in the presence of severe cervical spondylosis, we must express disagreement with the views of Allen,[8] who is prepared to make the diagnosis and perform a radical operation without the aid of myelography.

Treatment

If one views the pathological process as essentially a mechanical compressive disorder, relief and perhaps reversal of symptoms could be expected from surgical intervention. This may range from simple decompression by laminectomy, perhaps with division of dentate ligament as recommended by Kahn,[9] to a full-scale attack on the spondylotic ridge itself, with the object of restoring a smooth ventral wall to the spinal canal.[8] In fact, though the question causing most concern to the attending physician is whether he should advise his patient to submit to surgery, there is at present no clear answer to the problem. Nonetheless, on the basis of increasing experience, tentative broad conclusions may be advanced for application and consideration in individual cases.

CERVICAL SPONDYLOSIS AND COMPRESSION OF THE SPINAL CORD

Jackson Braham, M.C., M.D., M.R.C.P.
and
Eugene E. Herzberger, M.D., F.I.C.S., Tel Aviv, Israel

• *Indentation of the cervical part of the spinal cord by protrusion of intervertebral disks and by osteophytic lipping produces varied neurological symptoms directly by mechanical injury and indirectly by effects on the movement of blood and cerebrospinal fluid. Diagnosis depends on cerebrospinal fluid manometry and myelography, for the symptoms may have more than one cause.*

In one case, the extensive paralyses in the patient were found to result from amyotrophic lateral sclerosis in addition to osteophytes that had caused marked narrowing of the disk space at the fourth and fifth cervical levels. In a second case, gross spondylotic changes in the cervical region coexisted with a sarcoma that was blocking the canal completely in the thoracic region.

Laminectomy, with section of the dentate ligament, was done in six cases of chronic cord compression by cervical spondylosis. No improvement resulted in one case, and in two the results were hard to assess. But in three there was partial success, and two of these patients were relieved of symptoms and enabled to return to their occupations. This experience indicated that surgical treatment should be reserved for the patient in whom the symptoms are recent and rapidly progressing.

In recent years increasing attention has been paid to the role played by spondylosis in the production of cervical cord syndromes. Although as yet little or no mention is made of this subject in standard medical or neurological textbooks, a number of papers have emphasized its importance and frequency, particularly as a cause of disability in the older age groups.

Because of the ubiquity of cervical spondylosis in the general population and, in particular, among older people, there is an understandable reluctance to attribute neurological disturbances to this finding; however, as has been shown by Pallis and others [1] during an independent assessment of the radiological and neurological status in a group of elderly people, the connection is by no means fortuitous. It may well be, as these authors contend, that it is necessary to revise opinions about the "physiological" nature of various neurological findings in the senescent population. With the greater interest in this diagnostic possibility, certain general views have tended to crystallize with regard to problems of etiology, diagnosis, and treatment. These have been reviewed recently by Brain [2] on the basis of previous detailed communications,[3] and we, in this paper, wish to present some of these aspects as they have been met with in everyday neurological and neurosurgical practice. We are concerned here with cervical spondylosis as a cause of chronic cord compression and not of root pains only.

Pathological Mechanism

Gross indentation of the cervical cord by intervertebral disk protrusion and osteophytic lipping with local degeneration of gray and white matter has been described in postmortem studies by Bedford and others.[4] These findings probably represent the end-result in an extreme case, and in the more usual situation of the ambulant patient with moderate signs and symptoms it seems unlikely that a permanent state of severe cord compression exists.

We have been constantly impressed by the spinal manometric readings in our patients, where observations of pressure fluctuations have confirmed the findings, limited to cases of spondylotic compression, reported by Kaplan and Kennedy.[5] With the head bent forward, a free rise and fall is seen on jugular compression and release, whereas in moderate or especially in full retroflexion of the neck, partial or complete manometric block is observed. Direct visual confirmation of this phenomenon has been frequently obtainable on myelography, when the column of oil has been seen to be held up or deformed during retroflexion, a free passage being obtained on return of the neck to the normal or flexed position. This evidence clearly supports the contention that recurrent partial compression of the cord during the many opportunities presented by neck extension movements during everyday life represents the probable pathological mechanism responsible. The compression possibly operates via interference with circulation in the anterior spinal artery, and hence there is recurrent ischemia in the area irrigated by this vessel.

Again, one frequently encounters the acute cervical cord syndrome resulting from trauma in patients with previously asymptomatic cervical spondylosis. This syndrome was referred to by Brain [3] and emphasized with numerous examples by Symonds.[6] The type of trauma is often a fall on the face, and the acute onset, believed to be due to momentary crushing of the cord by osteophytic ridges during the concomitant forcible hyperextension of the neck, may be considered as representing a catastrophic shortening in time of the slow evolution referred to above.

Diagnosis

The patients' complaints are generally referred in a quite variable manner to disturbances of function in the limbs. Weakness of one or both legs, difficulty in climbing steps, stiffness, and a dragging gait have usually been present for months or years, and the patient is unable to recall the precise time of onset of his symptoms. Diffuse weakness in one or both upper limbs, with clumsiness in execution of fine movements, may be the presenting feature, and paresthesias are often complained of. Occasionally, disturbances re-

From the departments of neurology (Dr. Braham) and neurosurgery (Dr. Herzberger), Tel-Hashomer Government Hospital.

lated solely to an arm and leg on the same side may awaken suspicions of a hemiparesis of central origin. In some, progressive weakness culminating in severe paraplegia characterizes the picture, although relentless deterioration is not inevitable and stationary periods, or even episodes, of improvement may be reported, especially when there have been opportunities for rest in bed.

The physical signs are no less variable from case to case. In general, evidence of lesions of upper motor neurons supplying the lower limbs dominates the scene, and these changes are often bilateral, even when the patient's complaints are directed to one side of the body only. In the upper limbs, anomalies of the reflexes vary according to the site of the compression; inequality of briskness between the two sides in the presence of bilateral pyramidal signs in the lower limbs constitutes, when present, valuable evidence of a local cervical lesion. Sensory changes are even less constant, both in incidence and in variety. Diminished appreciation of pinprick in the lower half of the body may reach a level many segments below that of the compression. As the condition progresses, so may a gradual rise in this level be evident. Vibration sense in the toes is more commonly diminished than is superficial sensation. Detailed analysis of the subjective and objective sensory and motor patterns is available.[3]

Cerebrospinal fluid manometry has been referred to already, and, whenever performed with the flexion-extension technique described, it has invariably given confirmatory information. The fluid itself has shown no deviation from normal values, except for an occasional moderate rise in the protein content not exceeding 65 mg. per 100 cc. in our series. Myelography has been used to supplement or corroborate changes observed on plain films for accurate localization and for exclusion of other disorders. With a hyperextension technique,[7] no difficulty was experienced in concentrating the oil column in the cervical canal. Convincing evidence of local pressure by spondylotic ridges is thus obtained and most readily visualized in lateral films taken with the patient prone.

Differential Diagnosis

Radiological evidence of cervical spondylosis is very frequent in adults. Many of these people, perhaps the great majority, are free of complaints related to the nervous system, although perhaps objective changes are less rare than may be supposed.[1] It follows that great care must be exercised in attributing neurological signs and symptoms to this cause, even when it may seem anatomically appropriate.

From the review of the varied clinical picture that may result from cervical spondylosis as outlined above, it is clear that this disorder may easily be confused with disseminated sclerosis or subacute combined degeneration of the cord and, when sensory findings are absent, with amyotrophic lateral sclerosis, quite apart from other causes of cord compression, such as new growth. This confusion may operate as it were in both directions, as pointed out by Brain.[3] Thus spondylosis may be unrecognized as being the real cause of cord syndromes; it may be recognized and improperly invoked as the cause of disorders that are, in fact, degenerative; it may coexist with degenerative disorders and contribute in variable measure to the over-all clinical picture. The following representative case histories are illustrative of the diagnostic pitfalls inherent in such an ambiguous situation.

Case 1—Cervical Spondylosis Complicating Amyotrophic Lateral Sclerosis.—A 55-year-old man gave a history of weakness in the limbs of four years' duration. Beginning in the left hand, it had spread to the right side, and later to the legs, so that on admission he was completely bedridden and helpless. Gross atrophy of the small hand muscles was seen on both sides, with a lesser degree of wasting but considerable weakness of the more proximal muscles of the upper limbs. There was spasticity of the lower limbs, with extensor plantar responses. The deep reflexes in all four limbs were exaggerated, but there were no sensory changes. Fasciculation was widespread. Anterior and posterior osteophytes were seen on x-ray examination at C-4 to C-5, with marked narrowing of the disk space. Myelography revealed gross identation of the oil column at this level.

On further observation of this patient in the ward, a certain thickness of speech was discovered to be of fairly recent onset, according to his relatives. A very brisk jaw reflex was elicited, and there was gross fibrillation of the tongue; an opportunity to witness outbursts of uncontrollable laughter and weeping made certain that, whatever role was played in the total clinical picture by undoubted cervical cord compression, the patient certainly suffered also from amyotrophic lateral sclerosis.

Case 2—Cervical Spondylosis Complicating Compression of Thoracic Cord by Tumor.—A 52-year-old woman complained of increasing difficulty in walking for the previous six months, hitherto attributed to diffuse osteoarthritis. Examination revealed marked inequality of the biceps reflexes (those on the right being greater than those on the left) and increased tone in the lower limbs, with bilateral extensor plantar responses. Superficial sensation, vibration sense and position sense were somewhat impaired in the lower limbs, without any clear upper level. These findings were considered to be indicative of a mid-cervical lesion, and, indeed, gross spondylotic changes at C-4 to C-6 were appropriately evident radiologically; however, on lumbar puncture, there was complete manometric block in all positions of the head, and the fluid contained 100 mg. of protein per 100 cc., findings rather more decisively pathological than had been within our experience in spondylosis cases. Myelography resulted in the unexpected discovery of complete block at T-9, at which level compression by tumor (sarcoma) was disclosed at a subsequent operation. In this patient, the physical findings could very well have been explained on the basis of the undoubted cervical spondylosis, with unfortunate results if confirmatory myelography had not been performed. On the basis of this experience, which was repeated in another patient with high cervical compression due to a meningioma, again in the presence of severe cervical spondylosis, we must express disagreement with the views of Allen,[8] who is prepared to make the diagnosis and perform a radical operation without the aid of myelography.

Treatment

If one views the pathological process as essentially a mechanical compressive disorder, relief and perhaps reversal of symptoms could be expected from surgical intervention. This may range from simple decompression by laminectomy, perhaps with division of dentate ligament as recommended by Kahn,[9] to a full-scale attack on the spondylotic ridge itself, with the object of restoring a smooth ventral wall to the spinal canal.[8] In fact, though the question causing most concern to the attending physician is whether he should advise his patient to submit to surgery, there is at present no clear answer to the problem. Nonetheless, on the basis of increasing experience, tentative broad conclusions may be advanced for application and consideration in individual cases.

In 1953 and 1954, operations were performed by one of us (E.E.H.) on 6 of the 11 patients in whom the diagnosis of chronic cord compression by cervical spondylosis was made and in whom no question arose of an alternative explanation for the signs and symptoms. Apart from a clinical assessment of the patient's capacity to bear the operation, no special selection of suitability was made in our early cases, there being, in fact, no rigid criteria available. In each case, laminectomy was performed with the patient under general anesthesia, the laminas at the site of compression and those immediately above and below it being included. The dura was opened, the cord inspected, and the dentate ligaments divided bilaterally. It may be mentioned here that dorsal humping of the cord over the spondylotic ridge could usually be detected; pulsation was poor but increased after the dentate ligaments were sectioned. In one case, discoloration of the cord was noted at the level of compression. In no case of our series was a soft protrusion of the intervertebral disk found.

In two cases, the operation was an unequivocal success; the patients were relieved of symptoms and were able to return to their former occupations. In one case, no improvement whatever resulted. In the remainder, partial success was achieved with moderate regression of symptoms, although, in two of these, factors associated with personality and social background made assessment somewhat dubious.

Case 3—Long History, Gross Disability, No Improvement.—A 53-year-old man began to notice progressive difficulty in walking, which began 10 years before his admission. Within two to three years, he had become bedridden and remained so. Approximately two years after the onset of symptoms in the legs, he noticed weakness of the right hand, which later became useless because of contracture. Examination showed paralysis and atrophy of the muscles of the hand, with contractures of the fingers on the right; some weakness of small muscles was found on the left. The lower limbs presented the appearance of paraplegia in extension, with spasticity of a degree that could not be overcome passively. The abdominal reflexes were absent. No sensory changes were discovered. Gross spondylotic changes at C-4 to C-5 and C-5 to C-6 were seen radiologically. On lumbar puncture, partial manometric block was obtained on retroflexion of the neck; the fluid itself was normal. Myelography showed indentation of the contrast medium at the level of the cervical lesion.

At operation, after laminectomy at C-4, C-5, and C-6, the cord was found to be impaled over the ossified ridges. Breathing and arterial pulsation caused blanching of the cord; there was no free movement at this level. The dentate ligaments were sectioned. The patient claimed some increase of strength in the upper limbs postoperatively; there were, however, no objective signs of improvement after several months, and surgery was considered to have been of no benefit in this case.

Case 4—Well-Marked Signs and Symptoms, Short History, Considerable Postoperative Improvement.—A man, aged 50, was referred for investigation as having hemiparesis of suspected intracranial origin. His complaints were limited to the left side and consisted of weakness of the arm and leg, which had become progressively worse in the previous three months, until he was no longer able to work. Clinical examination, although confirming the marked weakness of the left limb, demonstrated, however, that all four limbs were involved. Abnormally brisk tendon reflexes were present in both arms, an extensor plantar response was found on the right, and position and vibration sense were impaired in the toes on both sides. Gross spondylotic changes were seen radiologically at C-5, C-6, and C-7; on lumbar puncture, manometric block was obtained on retroflexion of the head, and the fluid contained 65 mg. of protein per 100 cc. Myelography showed gross indentation and almost complete blocking of the medium at C-6 to C-7 during retroflexion and a lesser degree of compression at C-5 to C-6.

After laminectomy and dentate ligament section (C-5, C-6, and C-7), gratifying subjective and objective improvement was noted within a few weeks—in particular the disappearance of pathological reflexes in the toes, with the return of deep sensation. Fine movements in the left hand returned, and the patient was now well able to use thumb and fingers in fastening buttons, a procedure that he had formerly been quite unable to carry out.

Case 5—Short History, Moderate Clinical Signs, Excellent Response to Surgery.—A 48-year-old man, engaged in heavy physical work, had a six-month history of numbness, beginning in the right hand and later spreading to the opposite side. These sensations, felt chiefly in the finger tips, were constant and were followed a few weeks later by loss of power in the right upper limb. There were no symptoms referred to the lower limb. On examination, there was diffuse weakness in the right arm, bilaterally increased briskness of tendon jerks in the upper limbs, absent right upper abdominal reflex, and inconstant extensor plantar responses. X-rays of the cervical spine showed marked narrowing of the space C-4 to C-5. On lumbar puncture, manometric block resulted on retroflexion of the head. The fluid itself was of normal composition. Myelography revealed marked pressure on the cord at the level C-4 to C-5, and lesser deformity at C-5 to C-6 and C-6 to C-7 (see figure).

At operation, the laminas of C-4 to C-7 were removed bilaterally; marked spondylotic ridges were noted at C-4 to C-5 and C-6 to C-7, with a somewhat lesser elevation at C-5 to C-6.

Lateral cervic myelogram (case 5), with patient prone. Narrowing of the C-4 to C-5 interspace is seen, and, at this level, the oil column is held up by the posteriorly projecting osteophytic ridge. The film demonstrates the "tenting" effect of elevation of the dura by the ridge. A somewhat lesser degree of retroflexion of the neck, permitted immediately before this film was taken, allowed a few drops of the contrast medium to trickle in a cranial direction, and these are seen to mark the superior incline of the "tent" opposite C-4. Minor elevations are recognizable at C-5 to C-6 and C-6 to C-7.

The cord paled at each pulse and respiration; it remained immobile over these segments until the dentate ligaments were sectioned. Within a few weeks, the patient was completely free of his preoperative symptoms and signs and shortly afterward returned to his former occupation.

It will be noted that in patients at clinical extremes, as it were, the results of operations are such as might have been anticipated. The patients with short histories, with signs of cord involvement but as yet no crippling disability, did best; the bedridden spastic patient with a long history received no benefit. Intermediate cases were partially improved, and external factors were important in determining the patient's personal assessment. In general, we would consider it wise to recommend a preliminary period of observation; we advise intervention where deterioration is plainly evident both to the patient and to his medical attendant. The radical operation of total extirpation of the offending bony ridges has not been attempted on any of our patients. Although apparently a safe procedure in the hands of its chief advocate,[8] it is certainly a much more formidable operation than the conservative operation generally practiced, which, as is evident from the two latter case histories, may give perfectly satisfactory results.

Summary

Spondylosis of the cervical vertebrae may give rise to a syndrome of cord compression with a variety of subjective and objective neurological disturbances in the upper and lower limbs. These disturbances are believed to be due to repeated minor traumas of the cord during flexion-extension movements of the neck. In cases of cervical cord lesions due to spondylosis, an attitude of critical alertness in differential diagnosis is important, as shown by cases illustrating the possibilities of deception in this field. Myelography is indispensable in the avoidance of errors. Experience with surgical treatment suggests that this be reserved for the patient with a short history and a downhill course; surgical treatment does not seem advisable in the management of the patient with advanced paralysis. In cases suitable for surgery, satisfactory results are obtained by a conservative operation limited to laminectomy and section of the dentate ligament.

References

1. Pallis, C.; Jones, A. M., and Spillane, J. D.: Cervical Spondylosis: Incidence and Implications, Brain **77**: 274-289 (June) 1954.
2. Brain, W. R.: Spondylosis, the Known and the Unknown, Lancet **1**: 687-693 (April 3) 1954.
3. Brain, W. R.; Northfield, D., and Wilkinson, M.: The Neurological Manifestations of Cervical Spondylosis, Brain **75**: 187-225 (June) 1952.
4. Bedford, P. D.; Bousmquet, F. D., and Russell, W. R.: Degeneration of Spinal Cord Associated with Cervical Spondylosis, Lancet **2**: 55-59 (July 12) 1952.
5. Kaplan, L., and Kennedy, F.: The Effect of Head Posture on the Manometrics of the Cerebrospinal Fluid in Cervical Lesions: A New Diagnostic Test, Brain **73**: 337-345 (Sept.) 1950.
6. Symonds, C.: The Interrelation of Trauma and Cervical Spondylosis in Compression of the Cervical Cord, Lancet **1**: 451-454 (March 7) 1953.
7. Dalith, F.: Technic of Myelography in Cervical Lesions, Radiol. clin., to be published.
8. Allen, K. L.: Neuropathies Caused by Bony Spurs in the Cervical Spine, with Special Reference to Surgical Treatment, J. Neurol., Neurosurg. & Psychiat. **15**: 20-36 (Feb.) 1952.
9. Kahn, E. A.: Role of Dentate Ligaments in Spinal Cord Compression and Syndrome of Lateral Sclerosis, J. Neurosurg. **4**: 191-199 (May) 1947.

CLINICAL NOTES

THROMBOCYTOPENIC PURPURA RESULTING FROM SULFISOXAZOLE (GANTRISIN) THERAPY

REPORT OF TWO CASES

Thomas W. Green, M.D.
and
Julian Q. Early, M.D., Bristol, Tenn.

Reported blood dyscrasias resulting from sulfisoxazole (Gantrisin) therapy have been infrequent. This drug is considered one of the safest of sulfonamides for general use,[1] and we have been able to find only one other reported case of thrombocytopenic purpura due to therapy with sulfisoxazole.[2] However, in our own practice we have encountered the following two cases of this blood dyscrasia that are apparently related to the administration of sulfisoxazole.

Case 1.—A 69-year-old female was admitted to the Bristol Memorial Hospital on March 26, 1954, because of a purpuric skin rash of four days' duration. She had been treated in the past for hypertension, generalized arteriosclerosis, and osteoarthritis. On March 12, 1954, 2 tablets (0.5 gm.) of sulfisoxazole four times daily were prescribed for a urinary tract infection, making a total of 50 tablets over a period of one week. Three days after cessation of therapy and four days before admission she developed a generalized purpuric rash, which gradually became more pronounced and particularly marked over the legs. There was no other associated abnormal bleeding, such as melena, hematemesis, epistaxis, or bleeding gums. The temperature was 99.4 F (37.4C), pulse 84 per minute, respiration 20 per minute, and blood pressure 220/120 mm. Hg. Generalized purpura was present over the body, confluent in places over the legs. Ophthalmoscopic examination disclosed arteriosclerotic changes in the fundi without hemorrhages or exudates. The heart was enlarged to the left with a grade 2 systolic murmur over the apex. The aortic second sound was accentuated. The remainder of the physical examination was noncontributory. The hemoglobin level was 11.5 gm. per 100 cc., the red blood cell count was 4,200,000 per cubic millimeter, and the white blood cell count was 10,900 per cubic millimeter, with a normal differential. The corrected sedimentation rate was 22 mm. in one hour, and the hematocrit was 36%. The platelet count was 21,000 per cubic millimeter (indirect method), and the platelets appeared reduced to almost absent on Wright-stained smears of the peripheral blood. The clotting time (capillary tube method) was one minute and 30 seconds, and the bleeding time (ear) was prolonged. The tourniquet test (80 mm. Hg for five minutes) gave strongly positive results. The prothrombin time was 14.5 seconds, with a control of 14.5 seconds. The Kahn was negative. A catheterized urine specimen contained a trace of albumin, no sugar, and a normal sediment. Treatment during hospitalization was entirely symptomatic and supportive. Within two days the purpura began to fade and no new lesions appeared. The platelet count on March 30, four days after admission, had risen to 156,000 per cubic millimeter, and the purpura had largely disappeared. The patient was discharged on April 1, and no further bleeding phenomena or purpura had developed when she was last seen on Jan. 10, 1955.

Case 2.—A 64-year-old male was admitted to the Bristol Memorial Hospital on Oct. 27, 1953, because of vomiting. He had had epigastric distress intermittently for several years, usually relieved by milk or alkalis. This gastric discomfort had been persistently present for several weeks, and for two weeks prior to admission he had vomited frequently. For one week, he had been unable to retain any food. His temperature was 98.6 F (37C), pulse 92 per minute, respirations 28 per minute, and blood pressure 180/100 mm. Hg. He was a thin, elderly man, who appeared to have lost weight. The skin was dry and inelastic, and there was moderate pallor of the skin and mucous membranes. The heart was not enlarged; the sounds were of good quality; the rhythm was regular, and there were no murmurs or thrills. The remainder of the physical examination was unremarkable. Urinalysis showed a specific gravity of 1.014, absence of sugar, and 2+ albumin, and the sediment contained 25 to 30 white blood cells, 3 to 4 red blood cells, and occasional granular casts per high power field. The red blood cell count was 3,400,000 per cubic millimeter, hemoglobin level 9.0 gm. per 100 cc., white blood cell count 12,800 per cubic millimeter, and the differential was normal. The corrected sedimentation rate was 18 mm. in one hour, and the hematocrit was 24%. The nonprotein nitrogen level was 99 mg. per 100 cc., and the fasting blood sugar level was normal. Roentgenograms of the chest showed no pulmonary or cardiac abnormalities. Gallbladder series disclosed a poorly functioning gallbladder. Gastrointestinal series showed antral spasticity and irritability but no ulcer crater or deformity of the stomach or duodenum. Several small diverticula were seen in the descending colon on barium enema films. Skull roentgenograms were normal, and the electrocardiogram was essentially normal.

Initial hospital therapy consisted of intravenously given dextrose with saline solution and other symptomatic and supportive measures. He also received 2 pt. of whole blood without reaction. On Oct. 28, 2 tablets (0.5 gm.) of sulfisoxazole four times daily were given because of the pyuria. On Nov. 2, while the patient was still receiving sulfisoxazole therapy, he was found to have a generalized purpuric rash, and he began to bleed from the mouth, nose, and gastrointestinal tract. Use of the drug was immediately discontinued. The next day he passed several large tarry stools, became weak and faint, and the blood pressure dropped to 110/70 mm. Hg. The bleeding time was greater than 15 minutes, clotting time (Lee and White) 12 minutes, platelet count (indirect) 42,000 per cubic millimeter, clot retraction poor, and the tourniquet test was markedly positive. Smears of the peripheral blood showed that

the platelets were greatly diminished. The prothrombin time was 80% of normal. During the next several days, he continued to bleed from the gastrointestinal tract, necessitating a total of 19 transfusions to maintain a hematocrit between 25 and 30% during the period between Nov. 2 and Nov. 8. On Nov. 6 the platelet count was 39,000 per cubic millimeter, but it had risen to 229,000 per cubic millimeter by Nov. 8. The melena ceased between Nov. 7 and Nov. 8, and the purpura began to fade. On Nov. 8 the bleeding time was 30 seconds and the tourniquet test was negative. On this date the nonprotein nitrogen level was 115 mg. per 100 cc. In the interval between Nov. 8 and the day of discharge, there was no further purpura or melena. The hematocrit was 40% on the day of discharge, with the addition of two more whole blood transfusions. On Nov. 13 the nonprotein nitrogen level was 93 mg. per 100 cc., and the phenolsulfonphthalein excretion was 4% in 15 minutes and 16% in two hours. Pyelograms by the intravenous route were essentially normal except for poor dye concentration. The patient was discharged from the hospital on Nov. 17. He was last seen in the office on Jan. 21, 1954, at which time he felt well in general; the blood pressure was 170/100 mm. Hg, hematocrit 43%, nonprotein nitrogen level 71 mg. per 100 cc., and specific gravity on concentration tests 1.010. Urinalysis contained a trace of albumin, no sugar, and occasional white blood cells and granular casts.

Summary and Conclusions

It is generally thought that sulfisoxazole (Gantrisin) is one of the safest of all sulfonamides as far as blood reactions are concerned; however, the data presented in the two reported cases seem rather definitely to point to the serious complication of thrombocytopenic purpura developing with the administration of this drug. The patient in the first case recovered rapidly without any serious hemorrhagic difficulties after recognition of the disorder. The patient in the second case presented another version in that numerous transfusions were necessary to sustain his life until there was spontaneous recovery. Probably, sulfisoxazole is one of the safer sulfonamides as compared with some of the other drugs, as far as blood dyscrasias are concerned. On the other hand, it would seem obvious that this drug should not be used indiscriminately, but only when there are adequate indications.

Suite 2-H, Doctors' Building (Dr. Green).

References

1. Yow, E. M.: Observations on the Use of Sulfisoxazole (Gantrisin) in 1000 Consecutive Patients, with Particular Reference to the Frequency of Undesirable Side Effects, Am. Pract. & Digest Treat. **4**: 521 (Aug.) 1953.
2. Geiger, J.: Thrombocytopenic Purpura Induced by Sulfisoxazole (Gantrisin) Therapy: Report of Case Controlled by Platelet Transfusion, J. A. M. A. **149**: 1219 (July 26) 1952.

ELKOSIN IN THE MANAGEMENT OF URINARY TRACT INFECTIONS

Morton Bogash, M.D.
Helen Ellis, B.S.
and
John J. Murphy, M.D., Philadelphia

Despite the many new antibiotics that have been introduced during recent years, certain sulfonamide preparations still maintain a position of great usefulness in the management of urinary tract infections. Their high degree of effectiveness against the common invaders of the urinary system and their low cost, low toxicity, and ease of administration are a few of the reasons for their wide clinical acceptance.

From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, and the Department of Urology, Hospital of the University of Pennsylvania.

A recent modification of the basic sulfonamide radical toward greater solubility has led to the development and introduction of Elkosin [N¹-(2, 6-dimethyl-4-pyrimidyl) sulfanilamide]. Zeigler, Bagdon, and Shabica[1] in an in vitro solubility study of six therapeutically active forms of the commonly used sulfonamides found Elkosin ". . . clearly the most soluble drug in the entire sulfapyrimidine class in the pH range 4-7." Since infection tends toward a lowering of the urinary pH, this high solubility of Elkosin in the lower physiological ranges is of particular importance in diseases of the urinary tract. The studies of Prior and Saslaw[2] indicated that Elkosin was well absorbed, well tolerated, gave high blood levels, and was excreted within 48 hours with only 13 to 15% acetylation. Reports on the clinical effectiveness of the compound were also favorable.[3]

It was decided to undertake a study of Elkosin to evaluate its usefulness in the treatment of the common urinary tract infections usually encountered in an outpatient clinic of a large hospital. Patients with urinary tract infections, confirmed by urinalysis and urine culture, were treated without further selection. The drug was administered in doses of 1 to 1.5 gm. four times daily for one week. Urinalysis and repeat urine culture were obtained 24 to 48 hours after discontinuing use of the drug. If symptoms, urinalysis, or cultures revealed the infection to be persistent, the course of drug treatment was repeated for another week. Appropriate investigative studies were carried out during and after therapy. No other definitive therapy was employed except for dilatation of urethral strictures.

The patients were listed as cured if, after the course of treatment with Elkosin, they were asymptomatic, the urine was free of white blood cells and bacilli, and the culture was negative. Patients failing to meet any of these criteria or returning during the study with infection after a maximum of two weeks' therapy were listed as not cured. Results are shown in table 1. A

TABLE 1.—*Results of Elkosin Therapy in Eighty-One Cases of Urinary Tract Infection*

	Cured	Not Cured
Patients	28	53
%	34.6	65.4
Sex		
Male	9	15
Female	19	38
Obstruction		
Mild	8	5
Severe	...	5
Calculi	...	4
Tumors	...	1
Acute Infection	14	19
Chronic Infection	14	34

total of 81 patients were studied; 34.6% of these responded to Elkosin therapy. Thirty-three of the 81 patients had acute infections (by history); of these, 14, or 42%, were cured. Of 48 chronic infections (by history), 14, or 29%, responded. Obstructive uropathy was discovered in 18 of the patients. Ten of 18 patients with obstructive uropathy failed to respond. Failure also occurred in four patients with urinary tract calculi and in one with tumor.

The bacteriological flora encountered (table 2), is fairly representative of that usually reported in urinary tract infections. The usual resistance of Proteus vulgaris and Pseudomonas is well shown. The resistance

of mixed infections over those due to one organism is again emphasized. The listing of 12 secondary invaders demonstrates the tendency of resistant organisms to grow out when uropathy favoring persistence of infections exists. No serious toxic symptoms were seen. Therapy with the drug was discontinued in two cases because of nausea. Crystalluria was not detected in any patient during treatment.

Comment

Patients were considered cured only if (1) they were asymptomatic, (2) their urine was free of white blood cells and bacilli, (3) the urine culture was negative, and (4) they did not return for treatment during the course of the study. Considering the resistance of Streptococcus faecalis, P. vulgaris, and Ps. aeruginosa to treatment and the difficulties that usually present themselves in overcoming mixed infections in the urinary tract, the results with Elkosin may be interpreted as very good. When one pathogen was involved, cure was established in 18 of 30 patients. In 8 of 18 patients with obstructive uropathy cure was accomplished. Acute infections responded very well to Elkosin therapy. The over-all results indicate that Elkosin is of value in the management of commonly encountered urinary tract infections.

TABLE 2.—*Bacteriological Data in Eighty-One Cases of Urinary Tract Infections*

Organism or Type of Infection	In Patients Cured, No.	In Patients Not Cured, No.
Escherichia coli	10	36
Streptococcus faecalis	11	37
Aerobacter	2	6
Proteus vulgaris	1	6
Hemolytic Micrococcus pyogenes var. aureus	1	4
Hemolytic M. pyogenes var. albus	9	12
Pseudomonas aeruginosa	1	9
Gram-negative rod (unidentified)	1	...
Other streptococci	2	1
Fungus	...	1
One pathogen	18	12
Mixed infection	10	41
Secondary invaders	...	12

Summary

Twenty-eight patients (34.6%) of a group of 81 with unselected urinary tract infections were clinically and bacteriologically cured by treatment with 4 to 6 gm. of Elkosin [N¹-(2, 6-dimethyl-4-pyrimidyl) sulfamilamide] per day for 7 to 14 days. The usual bacteriological flora seen in urinary tract infections and infections complicated by obstructive uropathy, calculi, or tumor was noted. No serious toxic symptoms were encountered. We have found that Elkosin, one of the newer sulfonamides, is an effective addition to the physician's armamentarium in urinary tract infections.

3400 Spruce St. (4) (Dr. Bogash).

The Elkosin used in this study was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

References

1. Ziegler, J. B.; Bagdon, R. E., and Shabica, A. C.: The Solubility of Some Sulfonamides of Current Clinical Importance, Am. J. Digest. Dis. **21**: 74 (March) 1954.

2. Prior, J. A., and Saslaw, S.: Observations on Absorption, Distribution, and Excretion of Elkosin (N¹-[2,6-Dimethyl-4-Pyrimidyl]-Sulfanilamide) in Man; J. Lab. & Clin. Med. **38**: 420 (Sept.) 1951.

3. Phillips, C. A. S., and Lloyd, F. A.: Urinary Tract Infections: Experience with Elkosin, J. Urol. **72**: 1247 (Dec.) 1954. Commons, R. R., and Wire, T.: Clinical Evaluation of Elkosin in Refractory Genito-Urinary Tract Infections, Journal-Lancet **73**: 278 (July) 1953. Schloss, W. A.: Some Notes on Chronic Prostatitis, Connecticut M. J. **18**: 116 (Feb.) 1954.

COMMITTEE ON COSMETICS

Report to the Committee

This is the second in a series of two reports on the effects of the sun on the skin, which was prepared at the request of the Committee.

VERONICA LUCEY CONLEY, *Secretary.*

THE EFFECTS OF SUNLIGHT ON THE SKIN

Beatrice M. Kesten, M.D., New York

For centuries, men have recognized the therapeutic action of sunlight and have taken for granted that sunbathing increases man's energy and sense of well-being. Heliotherapy, however, was first advocated toward the end of the 18th century by Faure for chronic ulcers of the skin and by Chauvin for relief from apathy and anemia.

In 1877 Downs and Blunt discovered the bactericidal action of sunlight, and at the end of the century Finsen established that this action, as well as the production of sunburn, was caused by the invisible ultraviolet rays of the sun. With artificial light that imitated the solar spectrum and with sunlight, he and Bernhard pioneered in the successful treatment of diseases of the skin and other organs. In the 20th century the biochemical and physical properties of sunlight have been determined.

Apparently the conservative or rational use of sunlight or its artificial substitutes is healthful to most individuals, but the current habit of exposing to intense or prolonged sunlight considerable areas of the nonacclimated skin during the first days of the season is open to question. There is a notable seasonal incidence of temporary incapacitating sunburn and an increasing number of diseases caused or adversely affected by exposure to the sun's rays. In addition, chronic excessive exposure to the elements prematurely ages the skin and promotes development of keratoses and epitheliomas.

Distressing sunburns or other adverse effects on the skin frequently follow when the properties of solar radiation are disregarded. The intensity of the sun's rays reaching the earth's surface directly depends chiefly on the thickness of the atmosphere. Smoke, green foliage, and the brown earth absorb considerable sunlight, whereas water and dust scatter sunlight. In addition to direct solar radiation a great amount of the sunburn radiation is scattered by the sky, light clouds, or fog and reflected from surroundings. Sky radiation accounts for the severe sunburn that may follow sunbathing on a hazy or foggy summer day. Water, ice, and snow reflect sunlight, thereby increasing the dosage of a given exposure. The reflection of the sun's rays from the surface of water is twice as great as from a green field but only one-fourth as much as from fresh-fallen snow. The intensity of ultraviolet rays also varies with the time of day, season, altitude,

Assistant Professor of Dermatology, Columbia University, College of Physicians and Surgeons.

and latitude. Individuals most likely to suffer detrimentally from exposure to the sun are those with blue eyes, red hair, and fair skin.

The sun's rays of less than 2,900 A do not penetrate the atmosphere, and the biological action of wavelengths longer than 14,000 A in sunlight have not been sufficiently explored. In the continuous solar spectrum of electromagnetic waves with which we are concerned, ultraviolet rays fall between 2,900 and 3,900 A, visible light between 3,900 and 7,700 A, and near infrared between 7,700 and 14,000 A. About 1% of the sun's rays are in the ultraviolet range, and under optimal conditions only about 0.2% produce erythema. In winter, when the sun's position is low and toward the horizon, wavelengths of less than 3,000 A do not reach the northern part of the United States.

The erythema caused by the sun's rays is produced by strictly defined wavelengths of the ultraviolet between 2,800 and 3,132 A, the so-called sunburn range. Ninety to 95% of this erythemal radiation is absorbed by the normal white skin. In correlating the wavelengths of solar radiation with sunburn-producing potential, it was found that at 2,925 A erythemal effectiveness was 70%; at 2,967 A it rose to 100%; at 3,132 A there was a steep decrease to 2%. In experiments conducted in the Midwest, Luckiesh [1] determined that 20 minutes' exposure to the midday sun in June produced a minimal perceptible erythema on the average untanned white skin; 50 minutes' exposure was followed by a vivid erythema and pigmentation; and exposure for 100 minutes was followed by a painful sunburn.

After sufficient exposure to the sun, erythema appears after a latent period of 2 to 6 hours in the normal untanned white skin and usually reaches its maximum in about 10 hours. Depending on the exposure and the tolerance of the skin to sunlight, the response varies from a mild erythema to an intense sunburn with edema and blistering of the skin and systemic symptoms. Pigmentation usually begins with the subsidence of the sunburn erythema and is augmented by the concomitant exposure of the skin to the wavelengths between 3,300 and 4,400 A in the solar spectrum, because the long-wave ultraviolet rays darken preformed melanin granules. As the number of pigment granules in the deepest layers of the epidermis increase and migrate upward, they help protect against further sunburn. The natural skin oils and cellular debris on the surface of the skin offers only minor protection.

Thickening of the horny layer of the skin, subsequent to exposure, is thought to be the main mechanism by which accommodation to sunlight occurs. Not only does the horny layer absorb light strongly in the ultraviolet zone, but the flattened horny and granular layers of the epidermis reflect and scatter light. To a large extent this prevents the sun's rays from reaching the easily damaged deeper skin layers. Measurements of transmission of sunburn radiation by the skin suggest that a considerable degree of protection is afforded by relatively slight thickening of the horny layer.

Sweat also, owing to its absorption of wavelengths up to 3,300 A, provides some protection against sunburn. Goldring and co-workers have called attention to the presence of a substance in human sweat with intense absorption bands in the ultraviolet range that are capable of interfering with ultraviolet spectrophotometric readings.

In addition to the common sunburn, it is assumed that ultraviolet rays emitted by the sun enter into the pronounced persistent changes that occur in the skin of individuals, such as sailors and farmers, habitually exposed to wind and sun. In this heliodermatosis, excrescences and scaly erythematous lesions appear that could become malignant tumors.

Allergic eruptions caused by sunlight are not uncommon.[2] Intense inflammatory reactions may follow exposures that would cause no perceptible reaction in a normal skin. Urticaria and various types of dermatitis, occasionally associated with purpura, may appear after minimal exposure. Of particular diagnostic significance are the lesions, clinically indistinguishable from the early lesions of lupus erythematosus, that appear on areas exposed to the sun.

Chemicals such as porphyrins, eosin, other fluorescent dyes, and sulfanilamide photosensitize the skin to long-wave ultraviolet light and to visible rays. Of current interest are the rare reports of photosensitivity after oral administration of *p*-aminobenzoates, salicylates, chlortetracycline, stilbamidine, phenylbutazone, and antihistaminics, and the more frequent reports of sensitivity after chlorpromazine therapy. Sometimes the skin is sensitized to sunlight after repeated contact with certain plants, essential oils often found in perfumes and cosmetics, and coal tar pitch and its distillates. Recently Burckhart reported that a laundress developed an acute dermatitis of areas exposed to the sun after using a product claimed to transform ultraviolet to visible light, thus making the washing appear "whiter than white." The skin reactions to photosensitization tend to localize in areas exposed to the sun regardless of the route of sensitization. These eruptions have been deemed allergic because they can be reproduced by exposure to the sun, lesions were absent when the skin was protected from the sun, transferable skin-sensitizing antibodies were isolated in the serums, and successful desensitization was accomplished by graded exposure to sunlight.

In addition to producing sunburn allergies and photosensitization, sunlight may precipitate or aggravate a number of diseases. The often deleterious effects of undue sun exposure on persons with pulmonary tuberculosis are well known. Precipitation or provocation of lupus erythematosus has been suggested by the history of severe sunburn preceding the appearance of symptoms or the increase in severity of existing lesions after exposure to sunlight, by the predominance of lesions on areas exposed to the sun, by the increased incidence of lupus erythematosus during the months of greatest sunlight, and by the lower ratio of lupus erythematosus in Negroes, whose skin is less sensitive to sunburn than the white skin. In this disease, about one-fourth of the patients tested for light sensitivity were photosensitive, and lesions

characteristic of the disease were produced in a few patients after exposure to sun or ultraviolet light. In areas similarly exposed but protected by chemical sunscreening agents, experimental skin lesions did not appear. The administration of certain antimalarial drugs, which are sunscreening agents, is effective in the treatment of many persons with the discoid type of lupus erythematosus, but it is not known whether their therapeutic action has anything to do with their sunscreening effect.

Sunlight may precipitate a variety of lesions or pigmentation in patients with inherited skin diseases, disturbed porphyrin or endocrine metabolism, or severe malnutrition resulting from starvation or alcohol. Isomorphic reactions produced by the sun's rays occur occasionally in the eruptive stages of some skin diseases. In xeroderma pigmentosum, sunlight apparently promotes malignant changes in the skin.

The ingestion of antimalarial drugs such as quinine, quinacrine hydrochloride, chloroquine phosphate, and pamaquine have effectively controlled a number of eruptions caused or precipitated by sunlight. Chloroquine phosphate, given one to four times daily in tables containing 0.25 gm., is currently the drug of choice of most dermatologists. In specific instances the oral administration of one of the following drugs has suppressed light-sensitive eruptions: diphenhydramine hydrochloride, tripelennamine, crude liver extract, and estrogenic and gonadotropic hormones.

It has long been known that coating the skin with oils, with substances containing opaque powders, or with extracts from the bark of special trees offered some protection against sunburn. Thirty years ago Rothman demonstrated that *p*-aminobenzoic acid had an absorption band in the ultraviolet spectrum that embraced all sunburn rays. Later he and Rubin suggested the use of 15% *p*-aminobenzoic acid in Ruggles' cream, which is an effective antisunburn cream.[3] If a lotion is preferred, Bell[4] has suggested the following formula: 5% sodium *p*-aminobenzoic acid with 2% polysorbate 80 in equal parts of alcohol and water.

The so-called chemical sunscreens absorb at least 90% of the ultraviolet spectrum that produces sunburn.[5] They first appeared commercially in the U. S. in 1928 and now number well over a hundred. The more commonly used compounds are *p*-aminobenzoates, *o*-aminobenzoates (anthranilates), salicylates, cinnamates, hydroquinones, and tannic acid. More recently, digalloyl trioleate, said to be from the European black geranium, has been found effective in concentrations of 3 to 5%. Menthyl anthranilate, in concentrations of 5 to 15%, also has been used as a sunscreen, but its absorption of sunburn rays is relatively weak. Most dermatologists agree that cortisone and hydrocortisone are ineffective, as their absorption bands do not cover the erythemogenic region.

Some oily substances offer considerable protection from sunburn, as for example yellow petrolatum, which has a strong absorption band in the erythemogenic region. Oils extracted from seeds and nuts, such as sesame, peanut, and walnut oil, absorb a considerable percentage of the ultraviolet rays.

Further protection is afforded by opaque chemicals (sometimes referred to as physical sunscreens) that scatter light. The substances more commonly used, which depend on scattering properties rather than on absorption of ultraviolet light, are titanium dioxide, talc, kaolin, zinc oxide, and bentonite. Titanium dioxide scatters most ultraviolet rays between 2,900 and 3,900 A.

The ideal suntan preparation should be hypoallergenic, nonirritating, nontoxic, stable in sunshine, and should protect the skin from sunburn for three or four hours after application; it should also be nonstaining and reasonable in cost. Cosmetic chemists continue to strive for this ideal.

In the treatment of diseases produced or adversely affected by sunlight and requiring local protection, it is well to ascertain the individual's degree of intolerance, the most effective sunscreening agent, and the wavelengths that produce the abnormal reaction. To determine the degree of intolerance, small areas of the patient's skin are subjected to the midday sun, and the minimum time required to produce a perceptible erythema is noted. The most effective sunscreen may be then determined by applying various preparations to small areas of skin previous to testing with sunlight. An effective preparation should protect the skin from about 10 times the amount of sunlight that causes a perceptible erythema. By covering small areas of skin before exposure to the sun's rays with glass filters having known light transmittance curves, the approximate wavelengths producing abnormal reactions may be determined.

Although sunburn and many of the abnormal reactions to the sun's rays are caused by wavelengths of less than 3,100 A, other effects, such as porphyrias, sensitivities to fluorescent dyes, and the phytophotodermatoses, follow exposure to longer wavelengths of the ultraviolet range. Solar urticaria is unique in that it may be caused by the blue violet of visible light or by specific wavelengths within the ultraviolet range in different patients. In one case, near infrared rays were reported as having been urticariogenic. The various topical preparations that act as sunscreens against sunburn offer little if any protection against wavelengths beyond the ultraviolet spectrum.

References

1. Luckiesh, M.: Application of Germicidal, Erythemal and Infra Red Energy, New York, D. Van Nostrand Co., 1946.

2. Blum, H. F.: Photodynamic Action and Diseases Caused by Light, Am. Chem. Monograph, no. 85, New York, Reinhold Co., 1941. Epstein, S.: Allergic Light Dermatoses, Dermatologica **80**: 291 (Nov.) 1939; Studies in Abnormal Human Sensitivity to Light: Prurigo Aestivalis, Eczema Solare and Urticaria Photogenica: Report of 17 Cases and Review of Literature, J. Invest. Dermat. **5**: 187 (Aug.) 1942; Studies in Abnormal Human Sensitivity to Light: Light Sensitivity in Prurigo Aestivalis, Eczema Solare and Urticaria Photogenica: Report of Experiments, ibid. **5**: 225 (Oct.) 1942; Studies in Abnormal Human Sensitivity to Light: Passive Transfer of Light Hypersensitivity in Prurigo Aestivalis, ibid. **5**: 285, 289 (Dec.) 1942. Lamb, J. H., and others: Solar Dermatitis, Arch. Dermat. & Syph. **62**: 1 (July) 1950. Kesten, B. M., and Slatkin, M.: Diseases Related to Light Sensitivity, ibid. **67**: 284 (March) 1953. Zeligman, I.: Relationship of Porphyrin Metabolism to the Dermatoses, Thesis, Columbia University, New York, 1942.

3. Rothman, S., and Rubin, J.: Sunburn and PABA, J. Invest. Dermat. **5**: 445 (Dec.) 1942. Rothman, S., and Henningsen, A. B.: Sunburn-Protecting Effect of PABA, ibid. **9**: 307 (Dec.) 1947.

4. Bell, D., and Mazzone, W. F.: Prevention of Skin Damage by Sunlight, U. S. Armed Forces M. J. **3**: 1225 (Aug.) 1952.

5. deNavarre, M. G.: Chemistry and Manufacture of Cosmetics, New York, D. Van Nostrand Co., 1941. Giese, A. C., and Wells, J. M.: Sunburn Protection, Natural and Artificial, Scient. Month. **62**: 458 (May) 1946. Giese, A. C.; Christensen, E., and Jeppson, J.: Absorption Spectra of Some Sunscreens for Sunburn Preparations, J. Am. Pharm. A. (Scient. Ed.) **39**: 30 (Jan.) 1950.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION
Edited Under the Direction of the Board of Trustees
Editor and Managing Publisher . . AUSTIN SMITH, M.D.
Associate Editor . . . . . JOHNSON F. HAMMOND, M.D.
Editor for Medical Literature Abstracts . GEORGE HALPERIN, M.D.
Assistant Editor . . . . . WAYNE G. BRANDSTADT, M.D.

Subscription price . . Fifteen dollars per annum in advance
Cable Address . . . . . "Medic, Chicago"

DIRECT MEDICAL SUPERVISION OF REHABILITATION PROGRAMS

GUEST EDITORIAL

Frank H. Krusen, M.D.

In a previous editorial [1] in THE JOURNAL it was mentioned that "Rehabilitation may be defined as the process of assisting the handicapped person to realize his potentialities and goals physically, mentally, socially, and economically." Furthermore, it was noted that "Where rehabilitation centers have been established, they find it necessary to provide physiatrists; physical therapists; occupational therapists; speech and hearing therapists; clinical psychologists; nurses; a prosthetic service; vocational evaluation, counselling, and training service; social service; and a therapeutic recreation service."

In the state of Minnesota, for example, the board of health has determined that, at present, only two such complete centers exist. The board estimated also that eventually there should be one such center for each 300,000 to 500,000 population. Therefore, the state hopes finally to have seven such centers. It is recommended that rehabilitation centers be affiliated with community general hospitals and that there be direct medical supervision of all the ancillary workers in each center. In the Minnesota plan, in order to bridge the gap between the present shortage of rehabilitation facilities and the real need, six small "satellite" centers have been established, under medical supervision, in outlying communities. In no instance has a lay therapist in one of these centers been deprived of the direct medical supervision he requires, and the centers are so distributed that, with modern transportation facilities, no patient requiring rehabilitation need be deprived of the chance to receive it.

Delagi and his associates [2] have mentioned that "Recent articles on 'teamwork' in the field of rehabilitation have created conflicting concepts as to the role of the physician. . . . Not only are members of the allied professions, such as vocational counselors and psychologists, questioning the position of the physician as the inherent leader of the rehabilitation team, but patients, too, are becoming confused about their relationship with their physicians." They concluded that it is "fundamental in the philosophy and practice of medicine that physicians, not members of allied professions, are charged with primary responsibility for patient care."

It is desirable, then, to stress the need for direct medical supervision of rehabilitation centers or programs by competent physicians specially trained in the clinical aspects of care of the disabled and in the complicated techniques of physical, psychological, and social rehabilitation. Preferably, such a medical director should be a physiatrist (a physician trained in physical medicine and rehabilitation), but, since such specialists are in short supply, the director need not necessarily be a physiatrist. Any physician who is particularly interested in this field, such as an orthopedist, psychiatrist, or industrial physician, might direct such a center provided he will take the time to train himself in the clinical and technical aspects of the field and not leave these aspects of the work to lay persons who are not really trained for such medical responsibilities. If a physician who is not well trained in the clinical aspects of rehabilitation and who has not clearly determined his responsibilities attempts to direct such a program he may get off on the wrong track.

When groups planning new rehabilitation facilities attempt to organize their programs by employing a "coordinator" to bring together all the rehabilitation skills in a certain institution, they soon find that they must have a competent clinician well trained in all the techniques of physical, mental, social, and economic rehabilitation to direct their programs properly. Actually, the best solution is always to start with a well-organized medically directed department of physical medicine and rehabilitation and to coordinate all the rehabilitation activities through this department. As an example, one planner [3] of a new rehabilitation program finally decided that all that would be done for the untrained participating physician would be to make him "aware of what is available" and that "he himself would not provide it anymore than he would do biochemical determinations on his patients' blood." Still another coordinator [4] who is planning a rehabilitation program at a large medical center concluded that he should have a trained physiatrist directing all of the coordinated medical and ancillary rehabilitation services at his institution.

The patterns established in existing successful hospital programs for rehabilitation should be followed. The programs at Michigan University Hospital; Ohio State University Hospital; St. Francis and Methodist hospitals in Peoria, Ill.; the University of Minnesota Hospital; and Grace Hospital, Yale University, are good examples. A recent special issue of the journal *Hospitals* [5] discusses in detail the planning and actual construction of hospital rehabilitation facilities.

From the Section of Physical Medicine and Rehabilitation, Mayo Clinic, and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

1. Rehabilitation, editorial, J.A.M.A. **159**: 1540 (Dec. 17) 1955.
2. Delagi, E. F.; Abramson, A. S.; Ebel, A., and Brent, S. Z.: Teamwork in Medicine, Am. Arch. Rehabil. Therapy **3**: 7-11 (March) 1955.
3. Weir, D. R.: Personal communication to the author.
4. Beard, R.: Personal communication to the author.
5. Rehabilitation Facilities, Editorial Notes, Hospitals **30**: 55-60 (March 16) 1956.

Above all, when rehabilitation programs are being established, it should be remembered that, to be effective, they must have direct medical supervision of every phase of the program by a competent, specially trained physician who is a clinician and not just a coordinator. Despite the fine capabilities of the therapists, counselors, and other ancillary workers, such lay persons should never be permitted to assume responsibility for any of the medical diagnostic functions or to render clinical judgments regarding any rehabilitation procedures. While it is perhaps true that "rehabilitation is everybody's business," only a medical expert should direct a medical rehabilitation program.

BREAST FEEDING

For many years there has been an increasing tendency for mothers in the United States not to try to nurse their babies or to make a halfhearted attempt and give up within a few weeks. Pray and his coworkers [1] state that in a series of 3,700 infants only 34% were breast fed for over two months. Oberman and Burke [2] put the proportion even lower, especially in the northeastern states. The formulation of artificial feeding has been so perfected in recent years that Holt [3] says that there is no longer any nutritional advantage to prescribing human milk but that certain advantages to breast feeding remain. One of the chief of these lies in its freedom from bacterial contamination. It has the further advantages that it is economical and requires no elaborate preparation, improves the parent-child relationship, and is less likely to be associated with infant eczema and other allergic manifestations. There are practically no disadvantages, and breast feeding is contraindicated only if the mother has tuberculosis, severe debility, mastitis, or retracted nipples or if the infant has a harelip or cleft palate. According to Richardson [4] almost every mother can nurse her baby if she and her physician wish it and if she will learn the technique. What then are the reasons for failure?

Oberman and Burke state that the chief reason more mothers do not nurse their babies is that physicians and hospital personnel do not take the time to instruct them in its advantages and technique. Some physicians even discourage breast feeding. Newton and Newton [5] state that a physician's judgment regarding breast feeding is influenced not only by recent research findings but also by whether his wife breast fed his own children. Among some mothers an attitude that breast feeding is unfashionable or even shameful has sprung up; others believe that it will cause them to gain weight; and others fear that it will tie them down.

There is a psychosomatic reflex mechanism that influences the expulsion of already secreted milk in the breast, which is known as "let down." The Newtons,[6] in studying this phenomenon, found that women who were unsuccessful in nursing their babies had less complete let down than the successful mothers. Sucking is the primary stimulus to let down, but the reflex is also conditioned by the sight of the baby and anticipation of nursing. A self-demand schedule of nursing insures more vigorous sucking on the part of the infant, but if the baby does not get much milk the sucking vigor may traumatize the nipples. This inhibits the let down and sets up a vicious circle. This can, however, be prevented by giving the mother an injection of oxytocin prior to nursing, as this drug causes let down even in the presence of psychic inhibiting factors. In another study, the Newtons [7] observed the influence of the attitude of the mother toward nursing her baby on her ability to nurse. Those who wanted to or were determined to nurse their babies had a much greater degree of success, as was to be expected, than did those who were undecided or indifferent or those who gave up easily. However, attitudes were not influenced by previous experience with nursing or by the amount of milk the mother thought she had. The authors believe that at least three psychosomatic mechanisms influence the course of lactation: (1) the stimulation of sucking, (2) the let down, and (3) the blood flow to the breasts. The mother who is doubtful of her ability to nurse her baby successfully often allows less nursing time at each feeding, thereby greatly reducing the first factor; pain, fear, and emotional tension have been shown to inhibit let down; and the blood flow to the breast is likewise sensitive to emotional stimulation.

Richardson found that complete emptying of both breasts at each feeding is essential to maximal production, that heavy work cuts down production, that highstrung women are not good producers of milk, and that production normally increases until the baby is about 6 weeks old and then levels off. If the baby does not empty both breasts at each feeding, they should be emptied by manual expression. This also serves to show whether the baby is actually getting any milk and in most cases demonstrates to the mother that she does have milk. Although giving of complementary feedings at first may lessen the mother's anxiety, it also lessens the nursing vigor of the baby and Pray advises against it in the first four days. Exclusion of visitors while the mother is nursing is an aid to successful breast feeding in many cases. The consensus seems to be that many women who do not nurse their babies could do so successfully if a positive attitude toward this function were fostered early in pregnancy and adequate instructions were given. A revival of demand feeding rather than rigid adherence to a schedule is an aid to successful nursing. On the other hand, the mother who cannot nurse her baby, especially the primipara over 30 years old, should not be made to feel that she has failed as a mother.

---

1. Pray, L. G., Poindexter, M. H., and LeBien, W. E.: Breast Feeding: A Four-and-One-Half-Year Experience, J. Pediat. **47**: 68-72 (July) 1955.
2. Oberman, J. W., and Burke, F. G.: Infant Feeding, GP **11**: 79-86 (Jan.) 1955.
3. Holt, L. E.: Breast Milk, Cow's Milk and Infant Nutrition, Quart. Rev. Pediat. **10**: 79-89 (May) 1955.
4. Richardson, F. H.: Breast Feeding Comes of Age, J. A. M. A. **142**: 863-867 (March 25) 1950.
5. Newton, N. R., and Newton, M.: Recent Trends in Breast Feeding: A Review, Am. J. M. Sc. **221**: 691-698 (June) 1951.
6. Newton, N. R., and Newton, M.: Relation of Let-Down Reflex to Ability to Breast Feed, Pediatrics **5**: 726-733 (April) 1950. Newton, M., and Newton, N. R.: Let-Down Reflex in Human Lactation, J. Pediat. **33**: 698-704 (Dec.) 1948.
7. Newton, N. R., and Newton, M.: Relationship of Ability to Breast Feed and Maternal Attitudes Toward Breast Feeding, Pediatrics **5**: 869-875 (May) 1950.

MEDICAL NEWS

CALIFORNIA

Medical Tour of Soviet Union.—The California Medical Association will sponsor an official centennial tour of the Soviet Union and Europe, with departure from San Francisco and Los Angeles scheduled for Oct. 2 and return on Nov. 1 via Trans World Airlines. The tour will feature a four-day stopover in Paris en route to Helsinki in Finland and Leningrad and Moscow in the U. S. S. R., where meetings will be held with Russian physicians and other scientists. The group will return via Vienna, Austria; Rome, Italy; Madrid, Spain; and Lisbon, Portugal.

Information Meetings for Relatives of Mental Patients.—The State Department of Mental Hygiene and the San Francisco Mental Health Society are holding open discussions every Tuesday night, 7:30-9 p. m. at the San Francisco Mental Health Society office, 998 Eddy St. The meetings, led by a psychiatric social worker from the department of mental hygiene, cover pertinent information on the state hospital program, such as cost of care, visiting hours, and hospital policies and routines, as well as the type of patient cared for, treatment offered, and follow-up program after the patient leaves the state hospital. The groups are small and informal and offer ample opportunity for free discussion of questions. There is no charge. For further information, telephone Mrs. Joan Murray, San Francisco Mental Health Society, PRospect 6-4133.

DISTRICT OF COLUMBIA

Society News.—At the annual meeting of the Association of Former Internes and Residents of Freedmen's Hospital in Washington, D. C., Dr. Robert S. Jason, dean and professor of pathology at the Howard University College of Medicine, Washington, D. C., was installed as president. Dr. Jason has served the association for 20 years as secretary and assistant secretary. Guest speakers included Drs. Samuel A. Cosgrove, clinical professor of obstetrics, Columbia University, New York; John P. Caffey, Babies Hospital, New York; George E. Blackman, Roswell Park Memorial Institute, Buffalo; Robert A. Hingson, professor of anesthesiology, Western Reserve University School of Medicine, Cleveland; and Mark M. Ravitch, Baltimore City Hospital, Baltimore.

ILLINOIS

Grants for Mental Health Education.—Dr. Otto L. Bettag, Chicago, director of the Illinois Department of Public Welfare, recently announced the allocation of $559,280 to 26 agencies in the state for mental health education and community services for the fiscal year starting July 1. About 75% of these funds come from payments made under provisions of the Illinois Mental Health Code for care and treatment of patients in state mental hospitals and the remainder from federal mental health funds allocated to Illinois. Grants totaling $478,980 to 20 community mental health clinics throughout the state are included. The remaining funds were granted to six agencies carrying on mental health education programs and demonstration projects and providing professional training for staff personnel. The welfare department itself has an allotment of $15,800 in federal funds for training.

Chicago

Exhibit on Peacetime Uses of Atomic Energy.—An exhibit on the peacetime uses of atomic energy, "Atoms for Peace," was recently opened to the public at the Museum of Science and Industry, E. 57th Street and South Shore Drive. Assembled by the U. S. Atomic Energy Commission in cooperation with private American companies and organizations, this exhibit was especially prepared for the 1,400 atomic scientists from 72 nations who attended the International Conference on the Peaceful Uses of Atomic Energy in Geneva, Switzerland, 1955. It covers the major phases of the peaceful uses of atomic energy with models, demonstrations, instruments and devices, photographic transparencies, machines, and many actual atomic materials and elements. The exhibit includes medical instruments and instrument components, medical uses of atomic energy, industrial uses of radioisotopes, atomic preservation of foods, experiments in biology, and a demonstration of the naturally occurring radiation that constantly bombards the human body. How atomic materials are physically handled without danger is demonstrated by a mechanical manipulation operated by remote control. The museum is open every weekday from 9:30 a. m. to 5:30 p. m. Closing time on Sundays and holidays is 7 p. m. There is no admission charge to the museum or to the Atoms for Peace exhibit.

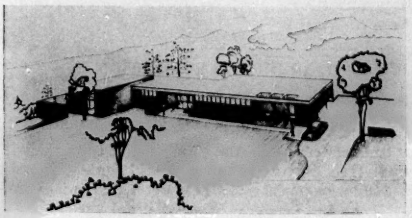
Society News.—The Chicago Urological Society recently elected Dr. Knowlton E. Barber, president; Dr. J. Lester Wilkey, vice-president; and Dr. Don E. Murray, secretary-treasurer.——Newly elected officers of the Metropolitan Dermatological Society of Chicago include Dr. James J. Barrock, Milwaukee, president; Dr. Cleveland J. White, vice-president; and Dr. Tibor Benedek, secretary-treasurer.——Newly elected officers of the Chicago Gynecological Society include Dr. Ronald R. Greene, president; Dr. Abraham F. Lash, president-elect; Dr. Charles Fields, vice-president; Dr. Robert A. Beebe, treasurer; and Dr. Clyde J. Geiger, secretary.

MINNESOTA

Retirement of Dr. Woltman.—Dr. Henry W. Woltman, who has served as Chairman of the A. M. A. Section on Nervous and Mental Diseases (1934) and as Secretary of the section (1931, 1932, and 1933), retired on July 1, after 37 years as a member of the staff of the Mayo Clinic, Rochester, on which he has been professor of neurology since 1931.

MISSISSIPPI

State Medical Headquarters.—At the centennial annual meeting in Jackson, the Mississippi State Medical Association dedicated and officially opened its first permanent home, the association's Central Office Headquarters Building at 735 Riverside Dr. In addition to ample office space, the building provides a 30-ft. conference room. Offices are connected with an intercommunication system and a centrally located electronic dictation system that operates through telephone instruments. Dr. S. Lamar Bailey, Kosciusko, the association's 1955-1956 president, delivered the dedication address, declaring that ". . . this building is more than a structure of masonry and steel. It is a lasting symbol of service, a tangible reminder of your doctor's dedication to you, not a monument, but a beacon which says every minute of the day and night that this is medicine in Mississippi—this is a symbol of service." In the dedicatory address, Dr. Bailey made reference to Solomon at the dedication of the Temple when he



New headquarters of Mississippi State Medical Association.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

said, "I have surely built Thee an house to dwell in, a settled place for Thee to abide forever." Dr. Guy T. Vise, Meridian, chairman of the association's council, presided as master of ceremonies. Drs. James Grant Thompson, Jackson, Stanley A. Hill, Corinth, and Louie T. Carl, Jackson, constituted the building committee. Dr. Bailey and Dr. Elmer Hess, Erie, Pa., then President of the American Medical Association, jointly cut the ribbon with gold suture scissors made especially for the occasion. Other distinguished guests included Dr. George F. Lull, Chicago, A. M. A. Secretary-General Manager; Dr. W. Raymond McKenzie, Baltimore, president, Southern Medical Association; and Dr. Arnold S. Jackson, Madison, Wis., president, International College of Surgeons.

NEW YORK

War Memorial Fund.—The Medical Society of the State of New York recently announced that the annual tuition awards under the War Memorial fund have been increased from $600 to $900. The War Memorial, which provides up to eight years of college and postgraduate education, has already benefited 27 of the children of the 25 members of the Medical Society of the State of New York who died in military service during World War II and the Korean war. It is estimated that 70 sons and daughters of these men will have become eligible for these grants by the year 1974, when the fund will have fulfilled its obligations.

University News.—The State University of New York College of Medicine at New York City, Brooklyn, has promoted from assistant professor to associate professor the following full-time faculty members: Dr. Irwin M. Murray and Jerome P. Parnell, Ph.D. (anatomy department); Dr. John D. Elder Jr. (department of anesthesiology); Drs. J. Leonard Brandt, Jacob Colsky, and Herbert C. Lichtman (department of medicine); Dr. Solomon A. Kaplan (department of pediatrics); and Dr. Melvin M. Newman (department of surgery). The following faculty members were promoted from instructor to assistant professor: Dr. Arlene R. Seaman (department of anatomy); Evelyn M. Witkin, Ph.D. (department of medicine); Drs. Harold R. Cottle and Philip H. Prose (department of pathology); Dr. Hugh M. Cardullo (department of pediatrics); Dr. Frederick F. Kao (department of physiology); Drs. James L. Curtis and Gerald Freiman (department of psychiatry); Drs. William Richardson and Jackson H. Stuckey (department of surgery); and Dr. Sidney R. Weinberg (division of urology).

Personal.—Dr. George E. B. Blackman, cancer research specialist on the senior staff of the Roswell Park Memorial Institute, has been honored by the Urban League of Buffalo for "outstanding achievement in community affairs." Dr. Blackman received the Professional Achievement award for his work in surgery and research at Roswell Park at the league's annual dinner.——Dr. Felix Martí-Ibáñez, associate editor of *Antibiotic Medicine & Clinical Therapy* and international editor of *Antibiotics & Chemotherapy*, has been appointed professor of the history of medicine and director of the newly established history of medicine department at the New York Medical College, Flower and Fifth Avenue Hospitals. Dr. Martí-Ibáñez is also editor of the *International Record of Medicine* and international editor of the *Journal of Clinical and Experimental Psychopathology*. Before coming to the United States in 1939, he practiced psychiatry in Barcelona, Spain, and taught medical history.——Dr. Ray K. Brown, who has been serving provisionally as assistant director for biochemistry and immunology in the division of laboratories and research, New York State Department of Health, Albany, has received permanent appointment to that position.

New York City

Institutes on Care of Premature Infants.—Institutes for physicians and nurses on the care of premature infants have been scheduled for Sept. 17 and Nov. 5, 1956, and Jan. 14, 1957 at the New York Hospital–Cornell Medical Center, under the sponsorship of the New York Department of Health and the United States Children's Bureau. Attendance at each institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses, four weeks. Participants pay no tuition fee, and stipends are provided to help cover expenses. If the number of applicants warrants, fourth and fifth institutes will be scheduled beginning March 11 and in early May, 1957. Additional information may be obtained from Box 143, Institute in the Care of Premature Infants, New York Hospital, 525 E. 68th St., New York 21.

University News.—At the 97th commencement exercise of New York Medical College, Flower and Fifth Avenue Hospitals, gold diplomas were awarded to the following graduates of the class of 1906: Drs. Sprague Carleton and A. Girard Cranch of New York City; Dr. Alfred C. Emmel, Mount Vernon, N. Y.; Dr. Frank S. Jameson, Hadden Heights, N. J.; Dr. Norman D. Mattison, Montclair, N. J.; Dr. Rupert S. Day, New Milford, Conn.; Dr. Judson G. Cottrell, Perth Amboy, N. J.; Dr. Harry C. Dumville, Niagara Falls, N. Y.; Dr. George H. Ding, Orleans, Mass.; Dr. William McLean, Durham, N. C.; and Dr. John H. Young, Pinehurst, N. C.

OHIO

Health Commissioner Positions.—The Ohio Department of Health announces the availability of several health commissioner positions for physicians. Information regarding locations, salary, and duties may be obtained from Mr. E. A. Graber, Bureau of Local Services, Ohio Department of Health, 306 Ohio Departments Bldg., Columbus 15, Ohio; phone CA 1-1265, ext. 341.

Course in Industrial Medicine.—If there is sufficient demand, the Institute of Industrial Health, University of Cincinnati College of Medicine, will present a course in industrial medicine for physicians of Cincinnati and vicinity during the second academic semester (two hours a week for 16 weeks or three hours a week for 11 weeks). The course will deal with the medical aspects of the industrial environment, recognition of hazards, treatment of industrial diseases, role and place of a plant medical department in an industrial organization, and the better use of community health resources, industrial psychiatry, and communication. The course (tuition fee $75) will be accepted by the Academy of General Practice for category 1 credit hour for hour.

PENNSYLVANIA

Health Conference.—The fifth annual Health Conference will be sponsored at the Pennsylvania State University, University Park, Aug. 20-23, by the Medical Society of the State of Pennsylvania, Pennsylvania Public Health Association, Pennsylvania Health Council, and the state department of health. In developing the conference theme, "Personal Responsibilities in Public Health," "Today and Tomorrow in Public Health" will be considered Tuesday morning by the heads of the four sponsoring organizations. Other topics to be discussed include "Health Education," "Contributions to Community Health," "Environment and Chronic Illness," and "Community Health Studies."

Philadelphia

Dr. Kolmer Feted.—A group of friends, colleagues, assistants, and former students of Dr. John A. Kolmer honored him on his 70th birthday, April 25, at the Alden Park Manor. Addresses were made by Dr. William N. Parkinson, dean, Earle H. Spaulding, Ph.D., professor of microbiology, Dr. Louis Tuft, and others of the Temple University School of Medicine and by Father John Curran, O. S. A. Among the physicians attending were Drs. Frank W. Konzelmann, Washington, D. C., W. Wayne Babcock, Claude P. Brown, Carroll S. Wright, S. Brandt Rose, J. Rudolph Jaeger, and Edward Weiss. Dr. Charles Weiss, head of the department of microbiology at the Albert Einstein Medical Center, a former student and research associate of Dr. Kolmer, who served as master of ceremonies, said, in part: "Much as one would like to dwell on your scientific achievements, it is more fitting in this age of anguish and anxiety to emphasize the influence which you have exerted on the personal lives and happiness of your students, associates and colleagues." Dr. Kolmer was presented with three volumes containing letters of greetings from his former research associates in Japan and from others in various parts of the United States.

WASHINGTON

Merrill Shaw Memorial Fund.—A revolving loan fund to aid undergraduate students who plan to become general practitioners has been set up at the University of Washington School of Medicine, Seattle, by the Washington Academy of General Practice in honor of the late Dr. Merrill Shaw of Seattle. Dr. Shaw had served as vice-president of the American Academy of General Practice and as a member of the board of directors. He was an organizer, charter member, and first president of the King County chapter and Washington Academy of General Practice. A gift of $1,000, presented as a nucleus, will be augmented by annual contributions from the Washington academy and, it is anticipated, by individual contributions. A goal of a $10,000 revolving, self-perpetuating fund has been set by the academy.

WEST VIRGINIA

State Medical Meeting.—The 89th annual meeting of the West Virginia State Medical Association will convene at the Greenbrier, White Sulphur Springs, Aug. 23-25, under the presidency of Dr. Athey R. Lutz, Parkersburg. Dr. Dwight H. Murray, Napa, Calif., President of the American Medical Association, will address the House of Delegates Saturday at 3:30 p. m. His subject will be "Federal Legislation and How It Affects the Medical Profession." Wednesday evening, Aug. 22, will be devoted to an open medicolegal meeting, moderated by Dr. William L. Cooke, Charleston. A panel discussion and question-and-answer period will follow addresses by former Governor Homer A. Holt, Charleston, and Dr. Walter E. Vest, Huntington, on problems of mutual interest to the members of the legal and medical professions, including malpractice and testimony in court. Motion pictures will be shown daily at 8:30 p. m. Thursday morning Dr. Carl B. Hall, Charleston, will serve as moderator for the following symposium on rehabilitation:

Hope in Rehabilitation, Donald A. Covalt, New York City.
Rehabilitation of the Cardiac Patient, Bernard J. Walsh, Washington, D. C.
Rehabilitation of the Mental Patient, O. Spurgeon English, Philadelphia.

A panel discussion, including a question-and-answer period, with the moderator in charge, will conclude almost all scientific sessions. Thursday afternoon a symposium on exceptional children will have as moderator Dr. Hiram W. Davis, Huntington, and as speakers Dr. Sarah L. C. Stevens, Huntington, Miss Frances A. Scott, Charleston; Drs. Covalt, Walsh, and English and Dr. Paul Gyorgy, Philadelphia. Cocktail hours, 6-7 p. m., have been arranged by the West Virginia chapter, Medical College of Virginia Alumni Association, and by Duke University School of Medicine Alumni, preceding the annual address of the president at 9 p. m. Friday morning will be devoted to the following symposium on obstetrics and gynecology, with Dr. Richard W. Corbitt, Parkersburg, as moderator:

Surgical Problems of the Female Pelvis, Virgil S. Counseller, Rochester, Minn.
Common Complications of Obstetrics, F. Bayard Carter, Durham, N. C.
Endocrine Problems of the Adult Female, Robert B. Greenblatt, Augusta, Ga.

Friday afternoon at 2 p.m. the West Virginia Society of Anesthesiologists will have as guest speaker Mr. William R. Huff, executive secretary, West Virginia Hospital Association, whose subject will be "The Hospital Administrator." At the same time an open meeting, section on internal medicine, West Virginia Diabetes Association, and West Virginia Heart Association, will hear "The Office Treatment of Anxiety States" by Dr. English; "Some Errors in the Diagnosis of Heart and Vascular Disease" by Dr. Walsh; and "Lupus Erythematosus" by Dr. Clarence S. Livingood, Detroit. At 2 p. m. also the West Virginia Obstetrical and Gynecological Society will have Dr. Carter as guest speaker. At 3:30 p.m. the Catholic physicians practicing in West Virginia will be addressed by the Rev. John J. Flanagan, S. J., executive director, Catholic Hospital Association, St. Louis. Scheduled for Friday evening are a cocktail party, University of Maryland School of Medicine Alumni (6:30-7:30 p. m.), entertainment by the woman's auxiliary (10 p. m.), and dancing in the ballroom. At the third general session, Saturday morning, "Commonly Missed Diagnoses in Skin Diseases" will be discussed by Dr. Livingood; "Factors Influencing the Spread of Cancer" by Dr. George Crile Jr., Cleveland; "Recent Advances in the Therapy of Diseases of the Chest" by Dr. Sol Katz, Washington, D. C. Dr. George F. Evans, Clarksburg, will be the moderator. At 1:30 p. m. Saturday the section on industrial medicine and public health will have as guest speaker Mr. Henry N. Doyle, assistant chief, Occupational Health Division, U. S. Public Health Service, Washington, D. C., who will present "Emerging Industrial Problems." At the same time the West Virginia Academy of Ophthalmology and Otolaryngology will hold a symposium on the eye, ear, nose, and throat. A joint meeting of the section on radiology, the West Virginia Society of Anesthesiologists, and the West Virginia Association of Pathologists has been scheduled for 2 p.m. to discuss the corporate practice of medicine in West Virginia and its ramifications in the light of the opinion of the attorney general on the subject. The West Virginia Pediatric Society will hear Dr. Gyorgy consider "Trends and Advances in Infant Nutrition," and the section on surgery will have as speaker Dr. Crile, whose subject will be "That Controversial Thyroid Nodule." Dr. and Mrs. Lutz will entertain members of the state medical association, auxiliary, and guests at a cocktail party at the Auditorium Terrace, 6:30-7:30 p. m. There will be dancing in the ballroom at 10 p. m.

Personal.—Dr. John Bankhead Banks of Charleston was elected president of the University of Virginia Medical Alumni Association at the meeting in Charlottesville early in June.—The following members of the West Virginia State Medical Association were recently elected to honorary life membership: Drs. Grover C. Morrison, Huntington; Cecil C. Jarvis, Clarksburg; and Marshall W. Sinclair, Bluefield; and Drs. Gustavus B. Capito, Henry M. Escue, and Ritchie A. Ireland, all of Charleston.—Dr. George M. Lyon, who recently became manager of the Veterans Administration hospital at Huntington, received from his alma mater, Denison University at Granville, Ohio, the honorary degree of doctor of science at the 125th annual commencement, June 11. Dr. Lyon's researches in 1940, relating to the use of drugs in the treatment of acute bacillary dysentery under the supervision of the National Research Council, resulted in the control of this disease by the British forces in the Middle East during 1941-1942.

GENERAL

Symposium on Hemophilia.—The National Hemophilia Foundation will present an International Symposium on Hemophilia at the Ambassador Hotel, Park Avenue at 51st Street, New York, Aug. 24-25. The tentative program includes the following presentations by foreign participants:

Surgical Treatment of Complications in Hemophilia, Erwin Deutsch, I. Medizinische Universität Klinik, Vienna, Austria.
Thrombocytography in Diagnosis and Management of Hemophilia, Pietro de Nicola, University of Pavia, Italy.
Parahemophilia (Prothrombin Accelerator Deficiency) Occurrence and Biochemistry, P. Fantl, Baker Medical Research Institute, Melbourne, Australia.
Insufficiency of Hemostasis in Hemophilia, Fritz Koller, Krankenanstalt Neumunster, Zurich, Switzerland.
Relationship of Hemophilia C (Rosenthal) and Hemophilia D (Spaet), Jean-Pierre Soulier, Centre National de Transfusion Sanguine, Paris, France (or Standardization and Tests of Activity of Antihemophilic Factors Used in Therapy).
The Marriage Problem and Descendants of Hemophiliacs, Alfredo Pavlovsky, Buenos Aires, Argentina.
Isolation, Stability, and Assay of Antihemophilic Factor in the Thromboplastin Generation Test, A. Winterstein, Basel, Switzerland.
Anticoagulant Excess as a Cause of the Clotting Defect in Hemophilia, Marc Verstraete, Louvain, Belgium (New York Hospital).

For further information concerning the symposium, contact Dr. Martin C. Rosenthal, National Hemophilia Foundation, 175 Fifth Ave., New York 10.

Biological Photographers.—The 26th annual meeting of the Biological Photographic Association will be held Aug. 27-31 in the Powers Hotel, Rochester, N. Y. The association, composed of scientific photographers concerned with the techniques and applications of photography in medicine, zoology, botany, and related fields, serves universities, medical schools, and hospitals. On Monday at a special daylong workshop on recent developments in materials and processes for color photography, lectures and demonstrations will be adapted to the limitations of the average medical or biological laboratory. The annual awards banquet will be held Thursday evening. Tours have been scheduled through the 550-acre Kodak Park Works of the Eastman Kodak Company and also the Bausch & Lomb Optical Company, with alternate tours through the medical photographic departments of the University of Rochester School of Medicine and Dentistry and the Rochester General Hospital.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States and its territories and possessions in the weeks ended as indicated:

Area	July 21, 1956: Paralytic Type	July 21, 1956: Total Cases Reported	July 23, 1955, Total
New England States			
Maine	..	..	5
New Hampshire	..	..	9
Vermont	1	1	1
Massachusetts	1	2	146
Rhode Island	..	..	4
Connecticut	1	1	20
Middle Atlantic States			
New York	9	20	42
New Jersey	1	4	12
Pennsylvania	..	5	12
East North Central States			
Ohio	8	17	35
Indiana	2	10	15
Illinois	42	80	19
Michigan	6	10	36
Wisconsin	7	11	40
West North Central States			
Minnesota	1	1	15
Iowa	3	20	24
Missouri	9	19	10
North Dakota	..	..	1
South Dakota	..	..	..
Nebraska	2	3	16
Kansas	3	7	6
South Atlantic States			
Delaware	..	..	1
Maryland	4	4	5
District of Columbia	..	..	5
Virginia	3	4	18
West Virginia	2	6	4
North Carolina	2	7	10
South Carolina	2	6	14
Georgia	7	8	6
Florida	5	14	7
East South Central States			
Kentucky	2	7	13
Tennessee	1	3	7
Alabama	2	2	8
Mississippi	4	7	7
West South Central States			
Arkansas	3	8	6
Louisiana	43	60	20
Oklahoma	1	6	18
Texas	31	61	89
Mountain States			
Montana	2	3	..
Idaho	..	5	7
Wyoming	1	1	3
Colorado	1	2	9
New Mexico	..	1	7
Arizona	3	7	1
Utah	..	6	..
Nevada	..	..	4
Pacific States			
Washington	1	1	5
Oregon	2	5	9
California	61	88	59
Territories and Possessions			
Alaska	no report	no report	..
Hawaii	1	3	2
Puerto Rico	..	..	2
Total	280	536	814

Postgraduate Medical Cruise.—The University of Texas Postgraduate School of Medicine has arranged with the Harvey Travel Bureau, 2005 W. Gray, Houston, for a postgraduate medical cruise to the Caribbean aboard the Antilles (French Line). The ship will leave from Galveston, Texas, Feb. 8 and return to Galveston Feb. 22, 1957. The ports of call include Port au Prince, Haiti; Kingston, Jamaica; Curacao, Netherlands West Indies; LaGuaira, Venezuela; Cristobal, Panama; and Havana, Cuba. Professors of surgery, internal medicine, pediatrics, cardiology, and obstetrics and gynecology will accompany the group. Details of the cruise may be secured from Mr. D. Stuart Godwin Jr., Harvey Travel Bureau, 2005 W. Gray, Houston, Texas.

CORRECTIONS

Research Fellowships and Grants.—Applications for postdoctoral research fellowships available July 1, 1957, will be received by the Life Insurance Medical Research fund until Oct. 15, 1956 (not Oct 1, as stated in the item entitled "Research Fellowships and Grants" in THE JOURNAL, July 21, page 1171).

Cancer of Cervix.—In the Query and Minor Note entitled "Cancer of Cervix," in THE JOURNAL, Aug. 4, page 1431, the second sentence should have read, "Schmitz and his followers (*Am. J. Obst. & Gynec.* **68**:494, 1954) use irradiation as the primary therapy and employ radical hysterectomy and pelvic lymphadenectomy when they have proof that the disease has recurred or persisted."

EXAMINATIONS AND LICENSURE

AMERICAN BOARD OF DERMATOLOGY: *Oral.* St. Louis, Oct. 12-15. Final date for filing applications was April 1. Sec., Dr. B. M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 15, 1956. Final date for filing application was May 1. *Oral Examinations in 1956.* New York City, Sept. 21-25. Final date for filing application was April 1. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Part I.* 1957. Applications for certification for the 1957 examinations are now being accepted. Candidates making new application or requesting the reopening of an application must do so before Oct. 1, 1956. Applications are to be accompanied by a list of hospital admissions. *Written. Part I.* Various cities of the United States, Canada and military centers outside the continental United States, Feb. 1. Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Practical Examination.* St. Louis, Oct. 20-24. *Written.* Jan. 21, 1957. Applications must be filed before July 1, 1956. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Oral. Part II.* Chicago, January 1957. Final date for filing application is Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Written and Oral.* Chicago, Oct. 8-11. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Written for Pathological Anatomy and Clinical Pathology,* Oct. 4-6. Final date for filing application is Sept. 1. Sec., Dr. Edward B. Smith, 1040-1232 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral, Part II.* New York City, Oct. 12-14, and San Francisco, Dec. 7-9. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: Miami, Oct. 17-19. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Oral and Written. Public Health.* Philadelphia, Nov. 8-10. Sec., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore, Md.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written.* Philadelphia, Sept. 29. Final date for filing application was June 28. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral,* New York, Dec. 10-11 and New Orleans, Mar. 18-19. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Los Angeles, Sept. 30-Oct. 4. Final date for filing application was June 1. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part I.* Various Centers Throughout the United States and in Certain Military Centers Abroad, Oct. 31. *Part II.* Buffalo, Sept. 24-25; Chicago, Oct. 15-16; New Haven, Nov. 19-20; Kansas City, Kan., Dec. 10-11; Los Angeles, Jan. 14-15; San Francisco, Jan. 17-18; Houston, Feb. 18-19; Nashville, Mar. 11-12; Boston, April 8-9, and New York, June 10-11.

AMERICAN BOARD OF UROLOGY: February 1957. Sec., Dr. William Niles Wishard, 1711 N. Capital Ave., Indianapolis 7.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, Sept. 7. Final date for filing applications was July 1. A subsequent written examination will be held in February 1957, and the closing date for registration is Dec. 1, 1956. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2.

DEATHS

Merritt, Edward Lester ✙ Fall River, Mass.; born in Fall River in 1894; Tufts College Medical School, Boston, 1917; member of the House of Delegates of the American Medical Association in 1938-1939; past-president and secretary of the Fall River Medical Society; member of the board of censors and past-president of the Bristol South District, Massachusetts Medical Society; member of the Fall River Historical Society; member of the American Urological Association, Association of Military Surgeons of the United States, American Public Health Association, and the American Cancer Society; served as vice-president of the Massachusetts Society for Crippled Children; in 1948 appointed on the advisory council of the Massachusetts Department of Public Health and for many years was public health officer in the Fall River area; veteran of World Wars I and II; past-commander of the Bristol County Council, American Legion, and a former state executive committeeman of the Legion; past-commander of the Narragansett Bay Chapter of the Military Order of World Wars; on the staffs of the Union, St. Anne's, and Fall River General hospitals; consultant at Newport (R. I.) Hospital and the Cape Cod Hospital in Hyannis, Mass.; long active in the Boy Scouts, held the organization's Silver Beaver award; formerly member of the board of directors of the YMCA; past-president of the advisory board of the Salvation Army; past-president of the Fall River Chamber of Commerce and of the Fall River Rotarians; a past-governor of the 197th district, Rotary International; served as a member of the board of trustees of Tufts College, Boston; member of the Boston Medical Library; attending physician, Home for Aged People; medical director of the Wentworth Manufacturing Company; medical examiner for life insurance companies; died May 4, aged 62, of hypertensive heart disease.

Kinney, Lyell Cary ✙ San Diego, Calif.; born in Johnstown, Wis., Sept. 5, 1884; University of Pennsylvania Department of Medicine, Philadelphia, 1908; after serving an internship at the German Hospital in Philadelphia, went to Los Angeles, where he was appointed radiologist at the California Lutheran Hospital; served as instructor in radiology at the University of Southern California School of Medicine in Los Angeles; veteran of World War I; one of the founders of the American Board of Radiology; member of the House of Delegates of the American Medical Association from 1932 to 1939 and from 1941 to 1943; past-president of the San Diego County Medical Society and president of the California Medical Association in 1930; past-president of the American Roentgen Ray Society; member and at one time vice-president of the American College of Radiology; member of the Radiological Society of North America and the American Radium Society; life member of the American College of Physicians; in 1931 initiated the formation of the cancer commission of the California Medical Association and served for several years as a member of the commission; from 1944 to 1948, was a director of the American Cancer Society and was instrumental in the establishment of the California division of that society; radiologist at Palomar Memorial Hospital in Escondido; died in Del Mar Feb. 1, aged 71, of injuries sustained when struck by an automobile.

Dixson, Ira ✙ Denver; born in Buffalo, N. Y., Sept. 4, 1901; Harvard Medical School, Boston, 1928; certified by the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Heart Association, the World Medical Association, and the American Diabetes Association; assistant clinical professor of medicine at the University of Colorado School of Medicine, Denver; served during World War II; on the staffs of the Denver General, Colorado General, and General Rose Memorial hospitals; founder of the Harvard University Medical Alumni Association; died in the Veterans Administration Hospital May 16, aged 54.

Newcomb, Kate Pelham ✙ Woodruff, Wis.; born in Wellington, Kan., in 1885; University of Buffalo School of Medicine, 1917; member of the American Academy of General Practice; her biography, "Dr. Kate: Angel on Snowshoes," by Adele Commandini was published in 1956; became nationally known when she appeared on a national television program, "This Is Your Life," in 1954; founder and chief of staff at Lakeland Memorial Hospital; on the staffs of the Sacred Heart Hospital in Tomahawk, St. Mary's Hospital in Rhinelander, and St. Mary's Hospital in Wausau, where she died May 30, aged 70, following an operation for fracture of the hip received in a fall.

Lanning, Charles Wesley, Herkimer, N. Y.; born in 1874; Syracuse (N. Y.) University College of Medicine, 1898; an associate member of the American Medical Association; past-president of the Otsego County Medical Society; for nine years Otsego County physician; formerly Tully physician and Onondaga County school commissioner; for many years practiced in Cooperstown, where he was on the staff of the Mary Imogene Bassett Hospital; on the staff of the Herkimer Memorial Hospital until his retirement in 1953; died in Richfield Springs April 18, aged 82, of generalized arteriosclerosis.

Broadfield, John Augustus, Philadelphia; Jefferson Medical College of Philadelphia, 1906; an associate member of the American Medical Association; died in the Northeastern Hospital May 20, aged 74, of carcinoma of the pancreas.

Close, John Burt, Mission, Texas; Ensworth Medical College, St. Joseph, Mo., 1908; died in the Mission Municipal Hospital March 19, aged 76, of arteriosclerotic cardiovascular disease.

Coe, Urling Campbell, Oswego, Ore.; Eclectic Medical Institute, Cincinnati, 1904; at one time secretary of the board of medical examiners of the state of Oregon; author of "Frontier Doctor"; died May 9, aged 74, of coronary insufficiency.

Cohen, Nathan ✙ Elmira, N. Y., Syracuse University College of Medicine, 1917; for many years school physician; on the staffs of the Arnot-Ogden Memorial and St. Joseph's hospitals; died May 3, aged 65, of leukemia.

Conklin, Alice Iva ✙ Dowagiac, Mich.; Northwestern University Woman's Medical School, Chicago, 1897; fellow of the American College of Surgeons; in 1919 member of the House of Delegates of the American Medical Association; for many years on the staff of the Women and Children's Hospital in Chicago; died in the Lee Memorial Hospital May 16, aged 87, of heart disease.

Coons, Samuel Gamble, Dry Run, Pa.; Jefferson Medical College of Philadelphia, 1894; past-president of the Franklin County Medical Society; on the staff of the Chambersburg (Pa.) Hospital; past-president and member of the board of directors of the Path Valley National Bank of Dry Run; died in Chambersburg April 1, aged 84, of coronary occlusion.

Cope, John Quincy, Lexington, Mo.; University Medical College of Kansas City, 1903; served as city health officer; honorary member of the staff of the Lexington Memorial Hospital; died in Columbia May 12, aged 86, of cerebral arteriosclerosis.

Copeland, Edwin King ✙ Woodland, Calif.; University of Oklahoma School of Medicine, Oklahoma City, 1930; member of the American Academy of General Practice; served during World War II; past-president of the Lions Club; on the staffs of the Yolo General Hospital and the Woodland Clinic Hospital, where he died April 18, aged 56, of coronary thrombosis.

Coppedge, Omer Clarence ✙ Bristow, Okla.; Barnes Medical College, St. Louis, 1905; died in Oklahoma City April 6, aged 76, of myocardial infarction.

Cordaro, Benjamin Joseph, Holbrook, Mass.; College of Physicians and Surgeons, Boston, 1941; member of the Massachusetts Medical Society; from 1950 to 1952 served in the Army Medical Corps in Germany; school physician; on the staff of the Goddard Hospital in Brockton; died in Manchester, Conn., May 6, aged 41, of injuries received in an automobile accident.

Corman, Morris David, Panorma City, Calif.; University of Minnesota Medical School, Minneapolis, 1942; interned at Northwestern Hospital in Minneapolis; died April 20, aged 62, of myocardial infarction.

✙ Indicates Member of the American Medical Association.

Corwin, Benjamin Frank, Brooklyn, N. Y.; Yale University School of Medicine, New Haven, Conn., 1897; an associate member of the American Medical Association; on the consulting staff of the Kings County Hospital Center; died April 4, aged 85, of cardiac decompensation.

Crabtree, Hillborn C., Lincoln, Neb.; Lincoln (Neb.) Medical College, 1916; died March 11, aged 73, of coronary thrombosis.

Crawford, William Barron ✙ Savannah, Ga.; Columbia University College of Physicians and Surgeons, New York City, 1899; at one time associated with the U. S. Public Health Service; member and past-president of the staff of St. Joseph's Hospital; served during World War I; died April 17, aged 80, of coronary thrombosis.

Crump, Walter Gray, Jr. ✙ New York City; New York Homeopathic Medical College and Flower Hospital, New York City, 1928; assistant clinical professor of surgery at the New York Medical College, Flower and Fifth Avenue Hospitals; fellow of the American College of Surgeons; on the staff of the Metropolitan Hospital; died May 9, aged 54, of a heart attack.

Dale, Charles Dorsey, Atoka, Okla.; Memphis (Tenn.) Hospital Medical College, 1904; past-president of the Atoka-Bryan-Coal Counties Medical Society; died in the Hendrick Memorial Hospital, Abilene, Texas, April 5, aged 76.

Daniel, Frank Charlton ✙ Pavo, Ga.; Emory University School of Medicine, Atlanta, 1929; died April 12, aged 52, of myocarditis and rheumatic fever.

DeMuth, Seth Ellis ✙ Hicksville, Ohio; Eclectic Medical Institute, Cincinnati, 1899; past-president of the Defiance County Medical Society; died May 11, aged 80, of arteriosclerotic heart disease.

Deutsch, Frederick, Euclid, Ohio; Medizinische Fakultät der Universität, Vienna, Austria, 1924; member of the Ohio State Medical Association; died March 31, aged 56, of coronary thrombosis, myocardial infarction, and arteriosclerosis.

Dinsmoor, Frank M. ✙ Keene, N. H.; University of Pennsylvania Department of Medicine, Philadelphia, 1893; served on the staff of the Elliot Community Hospital; died March 7, aged 87, of myocarditis, hypertrophy of the prostate, arteriosclerosis, and pneumonia.

Dixon, Ambrose ✙ Hennessey, Okla.; Gate City Medical College, Dallas, Texas, 1906; died April 11, aged 83, of myocarditis.

Doody, William Malachi ✙ Jersey City, N. J.; Fordham University School of Medicine, New York City, 1919; member of the American Psychiatric Association; director of the diagnostic clinic at Hudson County Hospital for Mental Diseases at Secaucus; died in the Jersey City Medical Center May 22, aged 61, of a heart attack.

Duffy, William Core, New Haven, Conn.; Johns Hopkins University School of Medicine, Baltimore, 1914; formerly assistant clinical professor of surgery at Yale University School of Medicine; fellow of the American College of Surgeons; served in France during World War I; consultant at Griffin Hospital in Derby; on the staff of the Grace-New Haven Community Hospital; died May 4, aged 67.

Edwards-Conover, Estella Mae ✙ Hyattsville, Md.; Bennett Medical College, Chicago, 1910; died in Bethesda April 28, aged 74.

Egger, Ernst, Chicago; Medizinische Fakultät der Universität, Vienna, Austria, 1922; on the staff of the Illinois Masonic Hospital; died in the Wesley Memorial Hospital June 2, aged 61, of lymphosarcoma.

Emmons, Charles Wallace ✙ Fairview Park, Ohio; University of Wooster Medical Department, Cleveland, 1906; member of the Cleveland Academy of Medicine; on the courtesy staff of Lakewood (Ohio) Hospital, where he died May 3, aged 73, of coronary thrombosis.

Estabrook, John Wesley ✙ Brandon, Vt.; University of Vermont College of Medicine, Burlington, 1895; died April 6, aged 84, of coronary thrombosis.

Feldman, Harold ✙ Pekin, Ill.; State University of Iowa College of Medicine, Iowa City, 1932; member of the American Academy of General Practice; served during World War II; associated with the Pekin Public Hospital, and the Methodist and St. Francis hospitals in Peoria; drowned in Carmel, Calif., May 20, aged 50, while attempting to save a woman swimmer from drowning.

Feldott, Harry Raymond ✙ Hinsdale, Ill.; Loyola University School of Medicine, Chicago, 1918; member of the American Academy of General Practice; formerly associated with the Veterans Administration in Hines; died May 27, aged 63.

Foty, Saviour R., Oak Park, Ill.; Jenner Medical College, Chicago, 1917; served on the staff of the West Suburban Hospital; died May 9, aged 77, of coronary thrombosis.

George, Joseph Cancianus, Pittsburgh; College of Physicians and Surgeons, Baltimore, 1910; died April 9, aged 81.

Gerhart, Margaret F. Welsh ✙ Mantua, N. J.; Woman's Medical College of Pennsylvania, Philadelphia, 1937; died April 7, aged 41, of coronary occlusion.

Giese, Charles Oscar ✙ Colorado Springs, Colo.; St. Louis University School of Medicine, St. Louis, 1905; first president of the American Academy of Tuberculosis Physicians; past-president of the Colorado Tuberculosis Association; formerly director of the National Tuberculosis Association; member of the American Trudeau Society; on the staffs of the Memorial, Glockner-Penrose, and St. Francis hospitals; formerly medical director of the Modern Woodmen Sanatorium in Woodmen; died April 24, aged 80, of arteriosclerotic heart disease.

Ginsburg, Jack Charles, San Francisco; Stanford University School of Medicine, San Francisco, 1954; resident physician at the Veterans Administration Hospital; served during World War II; died May 17, aged 30.

Goodlove, Paul Corydon, Detroit; Detroit Homeopathic College, 1907; died April 13, aged 76, of cerebral hemorrhage.

Goodman, James Monroe, Frederick, Md.; Hahnemann Medical College and Hospital of Philadelphia, 1902; an associate member of the American Medical Association; served as city and county health officer; died in the Frederick Memorial Hospital April 22, aged 82.

Googe, George William ✙ Rienzi, Miss.; Kentucky University Medical Department, Louisville, 1903; on the staff of the Community Hospital, Corinth, where he died May 24, aged 79, of mesentery cancer and ascites.

Gracey, Robert Ralph, Abington, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1924; died May 9, aged 56.

Graves, Amos Maverick ✙ San Antonio, Texas; Tulane University School of Medicine, New Orleans, 1928; fellow of the American College of Surgeons; veteran of World War I; on the staffs of Santa Rosa, Baptist Memorial, and Nix Memorial hospitals; died in the Nix Memorial Hospital April 6, aged 57, of heart disease and arteriosclerosis.

Greene, Claude Dean, Spencer, Ind.; Indiana University School of Medicine, Indianapolis, 1912; member of the Indiana State Medical Association; served as county health officer; died May 6, aged 70, of carcinomatosis and carcinoma of the rectum.

Greene, Inslee Blair ✙ Everson, Wash.; Johns Hopkins University School of Medicine, Baltimore, 1907; died in Bellingham May 11, aged 77, of arteriosclerotic heart disease.

Grover, Orie I. Messinger, Marion, Ind.; Chicago Homeopathic Medical College, 1883; the Hahnemann Medical College and Hospital, Chicago, 1908; died in the Marion General Hospital Feb. 3, aged 93, of cerebral vascular accident and arteriosclerotic heart disease.

Guiberteau, George Rinehart ✙ Jeanerette, La.; Louisiana State University School of Medicine, New Orleans, 1947; interned at Southern Baptist Hospital in New Orleans; died May 19, aged 32.

Hackett, Thomas Edward ✙ Jackson, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1911; veteran of World War I; for many years surgeon for the New York Central Railroad; on the staffs of the W. A. Foote Memorial and Mercy hospitals; died April 11, aged 68, of coronary thrombosis.

Hayes, Leslie Scott, Louisa, Ky.; Kentucky School of Medicine, Louisville, 1908; served as mayor of Louisa; veteran of World War I; formerly secretary of the Lawrence County Medical Society; member of the county board of health; died April 22, aged 73, of carcinoma of the transverse colon.

Higbee, Paul Albert, Minneapolis; Hahnemann Medical College and Hospital of Philadelphia, 1900; died March 29, aged 82, of bronchopneumonia.

Hildreth, Robert Dudley, Westfield, Mass.; Harvard Medical School, Boston, 1908; member of the American Medical Association; medical examiner for Westfield State Teachers College; from 1914 to 1949 associate medical examiner for Hampden County; past-president of the Hampden County Medical Society; school physician; for many years on the staff of the Noble Hospital; died in Point Pleasant, N. J., April 20, aged 73, of heart disease and arteriosclerosis.

Hope, Paul Taylor, Mercer, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1901; an associate member of the American Medical Association; veteran of World War I; served as county coroner and jail physician; at one time superintendent of the Mercer Cottage Hospital; died April 7, aged 78, of coronary thrombosis.

Horn, John William ✠ Lucedale, Miss.; Mississippi Medical College, Meridian, 1909; medical examiner for George County Draft Board during World War II; died May 2, aged 76, of pneumonia with complications.

Humphreys, David Granville ✠ Fernandina Beach, Fla.; Hospital College of Medicine, Louisville, Ky., 1896; past-president of the Nassau County Medical Society; formerly associated with the U. S. Public Health Service; on the staff of Nassau General Hospital; died March 16, aged 83, of acute coronary thrombosis.

Hummons, Henry Lytle ✠ Indianapolis; Medical College of Indiana, Indianapolis, 1902; died April 5, aged 83, of cerebral thrombosis and arteriosclerosis.

Hurd, Randolph Campbell ✠ Newburyport, Mass.; Harvard Medical School, Boston, 1897; formerly medical examiner; served as president of the Historical Society of Old Newbury; on the staff of the Anna Jaques Hospital; died May 1, aged 83, of arteriosclerosis.

Johnson, Peter Joseph, Brooklyn, N. Y.; College of Physicians and Surgeons, Baltimore, 1903; served as assistant health officer of the Port of New York; formerly superintendent of the Sea View Hospital in Staten Island and the Cumberland Hospital; died April 8, aged 80, of arteriosclerotic heart disease.

Johnson, Willard Judd, Decatur, Ill.; St. Louis University School of Medicine, 1904; died in St. Mary's Hospital April 18, aged 81, of duodenal and marginal ulcers with stenosis.

Kagane, Nathan ✠ New York City; Université de Gèneve Faculté de Médecine, Switzerland, 1924; on the staff of the Beth Israel Hospital; died April 22, aged 63, of coronary thrombosis.

Kalcounos, William Nicholas ✠ Pawtucket, R. I.; St. Louis University School of Medicine, 1939; interned at St. Mary's Group of Hospitals in St. Louis; twice president of the Pawtucket Medical Society; on the staff of the Memorial Hospital, where he died April 11, aged 43, of cerebral hemorrhage.

Katz, Joseph, Brooklyn, N. Y.; Long Island College Hospital, Brooklyn, 1914; at one time instructor in gastroenterology at the New York University Post-Graduate Medical School, New York City; on the staff of the Swedish Hospital; died March 19, aged 70, of acute coronary occlusion.

Kell, William Richard, Pascagoula, Miss.; Bellevue Hospital Medical College, New York City, 1890; formerly county health officer; died in the Jackson County Hospital April 24, aged 91.

Larrabee, Scott Goddard, St. Paul; Medical School of Maine, Portland, 1906; died April 2, aged 71.

Lawrence, Joseph Henry ✠ Brockton, Mass.; Bellevue Hospital Medical College, New York City, 1892; veteran of World War I; formerly member of the city board of health; for many years on the staff of the Brockton Hospital; died in the Goddard Hospital April 19, aged 85.

Lebowske, Joseph Arthur ✠ Minneapolis; Minneapolis College of Physicians and Surgeons, medical department of Hamline University, 1904; died in the Mount Sinai Hospital April 1, aged 75, of cachexia and cerebral arteriosclerosis.

Lee, Linford Henry ✠ Los Angeles; University of Nebraska College of Medicine, Omaha, 1921; member of the Association of Life Insurance Medical Directors of America, of which he was past-president; member of the American Heart Association; vice-president and medical director of the Pacific Mutual Life Insurance Company; died April 11, aged 60.

Lewis, Murney Edward, New York City; Columbia University College of Physicians and Surgeons, New York City, 1905; member of the Medical Society of the State of New York; veteran of World War I; on the staffs of the Bellevue, Lutheran, and Woman's hospitals; died April 27, aged 74, of hypertensive arteriosclerotic heart disease.

Lichtenfels, Frederick Victor ✠ Pittsburgh; University of Pittsburgh School of Medicine, 1912; formerly on the staff of the Eye and Ear Hospital; died May 6, aged 68, of coronary thrombosis.

Lieb, Charles Christian ✠ New York City; Columbia University College of Physicians and Surgeons, New York City, 1906; Hosack professor of pharmacology emeritus at his alma mater; served as secretary of the Association of the Alumni, Columbia University College of Physicians and Surgeons; member of the British and American Physiological societies, the Society of Pharmacology and Experimental Therapeutics, and the Society of Experimental Biology and Medicine; died April 6, aged 75, of carcinoma of the lung.

Lindig, Hesser Charles Clapham ✠ Glenside, Pa.; Temple University School of Medicine, Philadelphia, 1935; specialist certified by the American Board of Proctology; served during World War II; on the staffs of the Temple University Hospital in Philadelphia and the Abington (Pa.) Memorial Hospital, where he died April 11, aged 50, of carcinoma of the stomach and peritonitis.

McAlear, Lowell Eldred ✠ Berkeley, Calif.; University of Oregon Medical School, Portland, 1935; on the staffs of the Peralta Hospital and Children's Hospital of the East Bay in Oakland, and the Alta Bates Community Hospital; died April 15, aged 46.

McCain, Gilpin Montieth, St. Cloud, Fla.; University of Pennsylvania School of Medicine, Philadelphia, 1912; died March 16, aged 70, of senility.

McClung, Anna Mae Henry, Pattonsburg, Mo.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1899; died in Bethany April 22, aged 77, of cancer.

McCue, Christopher, Goodells, Mich.; Trinity Medical College, Toronto, Canada, 1890; died in Saginaw March 25, aged 87, of arteriosclerotic heart disease.

McNary, William Duncan, Milwaukee; Rush Medical College, Chicago, 1896; died April 15, aged 85, of a fractured hip.

MacKellar, Harry Rex ✠ Colonel, U. S. Army, retired, Vancouver, Wash.; Jefferson Medical College of Philadelphia, 1910; entered the Medical Corps of the U. S. Army in June, 1912; veteran of World War I; retired Jan. 31, 1943; died in Madigan Army Hospital, Tacoma, April 23, aged 77, of aneurysm.

Manning, Armas A. ✠ Los Angeles; Detroit College of Medicine and Surgery, 1935; certified by the National Board of Medical Examiners; member of the Industrial Medical Association; died April 23, aged 49, of cerebral hemorrhage.

Montague, Laurence Joseph ✠ Houston, Texas; University of Texas School of Medicine, Galveston, 1920; fellow of the American College of Surgeons; served on the staff of the Grandview Hospital in Edinburg; died March 18, aged 62, of coronary thrombosis and fracture of the hip.

Moreland, Edgar Wallace, Fort Wayne, Ind.; Central College of Physicians and Surgeons, Indianapolis, 1904; died March 23, aged 90, of arteriosclerotic heart disease.

Wenzlick, George John, Davenport, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1901; died recently, aged 77, of coronary occlusion.

FOREIGN LETTERS

AUSTRIA

Carcinoma of the Lips.—At the meeting of the Society of Physicians in Vienna on June 8, Dr. K. Wasserburger reported on three patients with carcinoma of the lower lip who had been treated 14, 9, and 5 years earlier. In all three patients the carcinoma was of the squamous cell type, and all three remained free of symptoms. Lymph nodes were palpable in all three when first examined, and in two patients the lymph nodes showed chronic inflammation. One patient had a spread of the carcinoma that was demonstrated when the lymph nodes were removed. Radium therapy of carcinoma of the lower lip yielded good permanent results. Reviewing the subject, the speaker said local recurrences have been reported in 10% of the cases. No deaths resulted from radium therapy. There were complications in less than 1%. Experience showed a definite drop in permanent results in patients with involvement of the regional lymph nodes, and consequently resection en bloc was performed in every case. Postoperative teleradium therapy was given, using 6,000 to 8,000 r. This procedure was of limited value in (1) the 21% of the patients in whom fixed lymph node tumors were found on the first examination, (2) patients of advanced age who therefore had a short life expectancy, and (3) patients in poor general condition and those who had other severe diseases.

It is difficult to decide in the individual case whether the enlarged lymph nodes are chronically inflamed or already changed by neoplasm. In doubtful cases operation should be performed early to give the patient the best chance. The operation should be performed before proliferation occurs through the capsule of the lymph node in the course of the transformation of the chronically inflamed submaxillary lymph node into a neoplastic node. In order to prevent centripetal spread, en bloc resection must be performed at once in carcinoma of the lip when a lymph node of the truncus jugularis is palpable in addition to a submaxillary lymph node. Dr. R. Ullik emphasized the occurrence of irradiation-resistant carcinoma. In such cases, the patients should be referred to the surgeon as soon as possible to avoid the necessity of resecting the inferior maxilla. Dr. J. Tappeiner stated that smaller carcinomas of the lip may be excised and in larger tumors studding with radium needles with a low charge may be practiced in order to reduce the necrotic tissue break-down adjacent to the needles. Studding permits adequate irradiation of the tumor without burdening of the cutaneous surface.

Circulation in Athletes.—At the same meeting, Drs. L. Slapak and L. Prokop reported that enlargement of the heart may be found relatively frequently, but not universally, in athletes. It develops gradually in the course of years and depends on the type of sport in which the athlete is active. The roentgenokymogram shows characteristic features in the heart of the athlete. In the area of the apex there may be either a lateral plateau formation or a silent zone instead of the normal sharp points. The latter may reappear after the load had been removed. In the electrocardiogram of well-trained athletes taken at rest, a prolonged PQ interval, flattened T waves, and a prolonged QT interval may be observed, depending mostly on a training vagotonia. These changes may return to normal after exertion.

It is the main task of the sports physician to determine in the described changes the borderline between normal and abnormal conditions, in order to recognize early damage and to prevent late severe lesions. Erroneous diagnoses must be avoided, so that normal persons do not become psychoneurotic. Electrocardiograms and kymograms taken after exercise and repeated roentgenologic and electrocardiographic control examinations will clarify the observations in doubtful cases. The prognosis of the athlete's heart is not unfavorable. Continued control by a sports physician is necessary, and the responsible supervisors (parents, teachers, or trainers) should receive adequate instructions. The various cardiac function tests are an important aid in evaluating the athlete's condition. Any standardized load placed on the heart may be used, but no single test satisfies all requirements. Tests of this type can be used only for relative evaluation. The most commonly used tests are the various knee-bending tests and modifications of the step test. The evaluation of the pulse and blood pressure alone may be unreliable, because these values vary in a compensatory manner. It is therefore advisable to use the products of pulse and blood pressure as is done in the so-called Vienna test. One unfavorable test is of very limited significance, because it may be the expression of a temporary disturbance or it may indicate a pathological change.

Suicidal Attempt with Insulin.—At the meeting of the Society of Physicians in Vienna on May 25, Dr. B. Königstein reported on a 27-year-old man with diabetes mellitus who was being examined at the department for diseases of metabolism of the City Hospital in Vienna-Lainz and who gave himself an injection of 2,000 units of protamine zinc insulin in an attempt to commit suicide. Since he had been observed when he gave himself the injection, he was admitted to the hospital without undue delay. He was given large amounts of carbohydrates, cortisone, epinephrine, and levarterenol, and thus a harmful drop in the blood sugar level and the occurrence of hypoglycemic coma was prevented. About 13 cases of suicidal attempts with insulin have been reported in the literature. In these, five persons died. One patient had to be institutionalized because of cerebral disturbances that resulted from prolonged hypoglycemic coma, and the remaining seven made a complete recovery.

Summer Camp for Diabetic Children.—At the same meeting Dr. W. Korp reported on the first Austrian summer camp for diabetic children, which was established in July, 1953, in the International Culture Home in Vienna-Hörndlwald. Only children with no serious developmental disturbances or complications were selected. It is believed that through community life diabetic children may be freed of the feeling of inferiority that often develops when they are thrown with children who have a normal metabolism. The speaker urged the establishment of homes for adult diabetics, as such homes have proved their value in other countries. Through their use the hospital stay of diabetic patients can be shortened and the patients can get much better training than that given in the hospital or in the course of ambulatory treatment.

Histology of Bone.—At the same meeting Dr. W. Lipp stated that bone undergoes changes by processes of transformation and renovation during the course of life. These processes concern the organic and inorganic elements of the bone. New microscopic and autoradiographic studies prove that, depending on physiological conditions, there is a direct relationship between the mineral content and the age of a bone; an uncalcified, malleable osteoid is not formed normally; osteomalacia cannot be demonstrated in the normal bone; and, during the entire life, there is a continued exchange of the mineral contents. The exchange of minerals occurs simultaneously with the processes of absorption and apposition but is partly independent of them. Recent experimental studies confirm the concept that bones serve not only as supportive organs to the entire body but also as a storage organ for minerals.

Regional Enteritis.—At the meeting of the Society of Physicians of Vienna on June 1, Mrs. I. Obiditsch-Mayer reviewed the histological findings of the surgical specimen of a 13-year-old boy from whom a 40-cm. loop of jejunum and a 40-cm. loop of ileum were removed because of intractable regional enteritis. The specimen showed an old inflammation with ulceration of the mucosa and with granulations and indurations in the intestinal wall. These processes caused constriction of the lumen. The degenerative changes in the innervation of the intestinal wall were accompanied, particularly in the granulation tissue and in the indurations of the submucosa, by extensive and presumably newly formed bundles of nerve fibers and extremely large ganglion cells. There were the well-known nodular tuberculoid structures in the intestinal wall, and in addition to this the

The items in these letters are contributed by regular correspondents in the various foreign countries.

vessels showed surprising, hitherto undescribed changes. Vessels of moderate caliber in the intestinal wall showed destructive changes sometimes accompanied by the formation of granulation tissue that contained giant cells. The changes in the small intestine that are typical of regional enteritis occurring in childhood were characterized both by proliferations of the nerve plexuses in the intestinal wall and by changes typical of a granulomatous giant-cell angiitis. These two criteria differentiated this process from other inflammatory intestinal changes and indicate that the process depends primarily on neurovascular changes.

Dr. Oppolzer stated that the myenteric plexus in patients with ulcerative colitis showed similar characteristics. Comparative studies on specimens from operation or autopsy of patients with ulcerative colitis and from patients with normal colons revealed greater density of the entire myenteric plexus in the former. The number of ganglion cells per cubic centimeter was three times as large in patients with ulcerative colitis as in those with a normal colon. Age, sex, or duration of the colitis did not influence the number of ganglion cells. This raises the question whether these changes in the myenteric plexus are a result of the disease or are a constitutional characteristic of these patients. Oppolzer believes that the changes in the myenteric plexus are primary and that only patients with this constitutional factor respond to neurosympathetic stimuli with colitis or enterocolitis. He believes that the myenteric plexus can be assumed to be of this nature in patients with excessive sensitivity to pressure of the abdominal aorta to the left and above the umbilicus or in whom sensitivity to pressure of the ileocolic artery simulates disease of the appendix. It is possible that histological changes exist also in the neurovascular plexus of the aorta and of the large abdominal vessels.

Intraconchal Transfusion.—At the same meeting Dr. W. Nissel and Dr. W. Rieder said that blood transfusion by way of the cavernous tissue of the lower nasal concha, or "intraconchal transfusion," can be used for the intravenous infusion of blood in patients in whom the veins are in poor condition or inaccessible. It will do away with venesection or with the dangerous intrasternal or intra-arterial methods. Intraconchal transfusion is easily performed and makes possible the intravenous administration of blood in large quantities in a relatively short time. This method is generally not advisable, however, in emergencies when blood must be given quickly.

Exercises for Urinary Incontinence.—At the meeting of the Austrian Society of Gynecologists and Obstetricians in Vienna on May 8, Dr. A. H. Palmrich reported on a method of controlled pelvic floor exercises with the aid of a vaginotonograph. The apparatus consists of a rubber bulb that is inserted into the vagina and is connected with a manometer and a writing apparatus. The patient herself observes the oscillations that depend on the contractions of the abdominal muscles and the muscles of the pelvic floor. Thus she can objectively determine the progress of her training even before improvement occurs in her ability to hold her urine. Preoperative and postoperative exercises should be performed by all patients who undergo operations for prolapse of the uterus. It is essential for the success of the treatment of incontinence to teach the patient to contract the muscles of the pelvic floor until a conditioned reflex is established.

Complications After Wertheim's Radical Operation.—At the same meeting Dr. F. Brandstetter stated that in women who undergo Wertheim's radical operation the urinary organs are exposed to great risk as compared to those in patients who undergo other gynecologic operations. The reasons are found partly in the close relationship between the internal genital organs and the urinary system and partly in the required technique of the operation and the nature of the disease for which the operation is performed. Modern anesthetic techniques, the improved methods of treatment of shock, and use of antibiotics make it possible to repair the urologic damage caused in patients by Wertheim's operation. D. J. Spurny stated that in his series of 690 Wertheim's operations 45 necrotic fistulas (6.5%) occurred. There was no visible damage to the ureter since the ureter was not even touched by the anatomic forceps. The high incidence of fistulas (9%) mentioned by Professor Knaus was observed between 1947 and 1950. There were also years with an incidence of fistulas of only 2%. The variable numbers of fistulas result from the respectively small numbers of cases. An incidence of 6.5% is within the limits of the larger statistical studies. Dr. T. Antoine said that the 9% incidence of fistulas was very high, but it was only temporary. Unfortunately one cannot always predict whether a fistula will occur, because occasionally everything goes well with a completely denuded ureter and in other patients a necrotic fistula may develop in a ureter that is completely in contact with the tissues. Avoiding contact with the ureter undoubtedly helps to prevent fistulas.

DENMARK

Mutual Aid for Physicians.—Benevolent organizations concerned with physicians and their relatives in distress often find the demands made on them far greater than the available funds. One such organization in Denmark has at its disposal about $5,800 yearly for distribution among so many physicians' widows that each can receive only a pittance. The plan has now been launched with the approval of the Danish Medical Association of issuing a special stamp to be affixed to envelopes containing physicians' bills and letters. A new stamp is to be designed every year. The stamps are colored red, blue, or green and are sold for about one cent each. They inform the recipient that the sender is a member of the Danish Medical profession, and they are a reminder of the obligations of every Danish physician to his less fortunate colleagues and to their widows and orphans. There are about 5,000 Danish physicians, each of whom sends out at least 1,000 letters every year with bills and other medical communications. The physician who spends $7 or more on these stamps need report only half the sum as taxable income. When this plan is put into force wholeheartedly, there should be an annual revenue of about $33,640 available for needy persons instead of the paltry sum now available.

Quinacrine for Lupus Erythematosus.—Dr. E. Harslöf (*Nordisk medicin*, June 14, 1956) has had both encouraging and disquieting experiences with quinacrine in the treatment of disseminating lupus erythematosus. A woman aged 66 was given 100 mg. of the drug three times daily, the dosage being reduced to 100 mg. daily after nine days. This dosage was continued for two months, and there was a gradual and marked subsidence of the rash and the chest pain and a return of the temperature to normal. Occasional recurrences of the rash were dealt with by giving another course of the drug and on one occasion by replacing the quinacrine with chloroquine. Another patient, a woman aged 58, responded very well at first but, after a total dose of 27 gm. of quinacrine had been given in the course of about 3½ months, a fatal case of pancytopenia developed.

Treatment of Mania with Lithium.—Dr. Mogens Schou in *Nordisk medicin* for June 7 stated that it was unfortunate for the first sponsors of lithium therapy that its introduction into psychiatric use coincided with that of chlorpromazine and reserpine, whose often dramatic effects have overshadowed such a cheap and homely remedy as lithium carbonate, yet within its modest indications, chiefly chronic forms of manic-depressive psychosis, lithium has many advantages. Schou gives lithium carbonate in 0.3-gm. tablets. When the drug is refused in tablet form, it may be introduced into a mixture made tasty by other ingredients. The initial dose consists of two tablets given two or three times a day, with a reduction to one tablet three times a day after a week or two. To prevent toxic side-reactions, the patient is supplied with an aqueous solution of sodium chloride. Even in therapeutic doses, lithium frequently induces a fine tremor of the hands that can be safely ignored as long as it is not marked. Early in the treatment there may be nausea, vomiting, and diarrhea. These reactions usually subside in a few days when the dosage is reduced. Some patients complain of giddiness, uncertainty of gait, and dryness of the mouth, all of them also calling for a reduced dosage. Sodium chloride given by mouth counteracts these symptoms, and it may be well to withhold this treatment when the kidneys and heart are diseased. Compensating for these shortcomings is the great advantage that lithium, given under close observation, can be administered over a long period, and Schou claims that no late effects have been observed following the continuous administration of lithium carbonate for more than three years. In 69 of 85 manic patients treated with lithium the manic symptoms abated or disappeared under this treatment. It is particularly useful in patients in whom chlorpromazine and reserpine have failed.

Return of Microsporosis.—The last serious outbreak of microsporosis in Denmark was reported on in 1907, and since then little has been heard of this highly infectious disease of the hair and skin, but following World War II it has appeared with growing frequency. Dr. Margrethe Gade in *Ugeskrift for laeger* for May 24 stated that 66 of a series of 67 cases were due to infection with Microsporum lanosum. In only one patient was the infection due to Microsporum audouini, the type most often affecting human beings. In all 67 cases the diagnosis was confirmed by direct microscopy and culture. In recent years the diagnosis of this disease has also been facilitated by the employment of ultraviolet light (Wood's light). In only 46 patients could the source of the infection be discovered, the offending vector usually being a cat or dog. In nine there was a possibility of infection from a human source through a schoolmate or other person. From the epidemiological point of view, these cases were most troublesome, partly because it was difficult to assure uninterrupted treatment and supervision. Some patients absented themselves from treatment, and others could not be traced. The results of treatment were unsatisfactory, and, in view of the poor results obtained with newest antimycotics, no use was made of them. The usual procedure was the application of local remedies containing sulfur or iodine. In only five cases was epilation by x-ray attempted. The duration of treatment ranged from three weeks to six months.

INDIA

Provincial Medical Conference.—The ninth Gujrath and Saurashtra Provincial Medical Conference was held at Navsari in May. The Minister for Finance, Prohibition, and Industries for Bombay said that only by nationalization of the medical profession can physicians best help the development of socialism. The first step in this regard has been taken by the introduction of the Employees' State Health Insurance Act. The scope of this act has to be expanded gradually so as to absorb all workers. As a first step all teaching posts in medical colleges and hospitals associated with them should be put on a full-time basis. The next step is to bring medical care to the rural population. A bonus should be given to those physicians and nurses who are transferred to rural areas.

Medical Research in the Second Five Year Plan.—The medical research objectives of the second five year plan included (1) strengthening the research facilities in existing institutions, (2) creating new institutes for research in specific fields, (3) training of research workers by a system of fellowships and by other means, (4) providing opportunities for the maximum display of talent of research workers, (5) creating conditions by which young and promising scientists may be attracted to a career in research and by which they may be induced to remain in research, (6) initiating programs for the solution of the many urgent problems in the field of medicine and public health, and (7) maintaining close cooperation with national and international agencies in all matters pertaining to research.

College of Physicians and Surgeons.—A special meeting of the College of Physicians and Surgeons of Bombay was held in June, at which time Prime Minister Nehru stressed the urgent need for free medical service and said that this could not be provided without help from the state. In spite of a number of good hospitals in Bombay, there is little doubt that the poor do not always get the same treatment as do the rich. Many of them cannot afford the expensive medicines prescribed by the physicians. The poor should get proper treatment whether in or out of the hospital. To this end, the medical profession should organize on a state basis so as to bring medical care to all the people and, more important, drugs should be manufactured by the state. Following his address Mr. Nehru was made an honorary fellow of the college.

NETHERLANDS

Blood Alcohol Determination.—The government is considering the introduction of a law by which punishment for excessive consumption of alcohol on the public highways would become more severe. At present driving a car when under the influence of alcohol is only forbidden, and the driver causing an accident is free to refuse to have his blood tested for alcohol content. The legislature now proposes to make this test compulsory in the future and to penalize a driver who, although not obviously under the influence of liquor, has nevertheless consumed an amount capable of reducing his ability to control his car. For practical reasons the government wishes to establish the critical level at an alcohol content of 0.05%. Although driving with the above blood alcohol content would not in itself be punishable, causing an accident under these conditions would be. The cooperation of the physicians is required in the enforcement of such a law. The Royal Netherland's Medical Association believes there are serious objections to their cooperating in the enforcement of this law, because a physician in his treatment of his patients must be governed by the following principles: (1) no procedure may be performed for which no direct medical indication exists or which is not meant for the benefit of the patient; (2) a procedure may be carried out only when the patient gives the physician his voluntary consent; and (3) the physician may perform only those procedures the consequences of which he completely recognizes.

In the execution of the above-named legislation it may be noted, first, that, although a venipuncture is in most cases easily performed, it is in some cases successful only after repeated attempts and at the cost of sizable hematomas. In the second place, the possibility of the development of serum hepatitis must be considered. Furthermore small irregularities in the puncture procedure or in laboratory determinations can be responsible for faulty results.

Infant Mortality.—In *Nederlandsch tijdschrift voor geneeskunde* (100:1742, 1956) J. H. de Hass reports that in 1955 the infant mortality in the Netherlands was reduced to 20 per 1,000 live births as compared with 104 in 1900 and 51 in 1930. In 1954 the infant mortality in Sweden was 18.5 per 1,000, in Scotland about 30, and in Western Germany and Belgium more than 40. In 1955 the mortality in various provinces in the Netherlands varied between 15 and 26 per 1,000. The decrease in mortality in the first week of life is still relatively slow, but there are many signs that the total infant mortality will continue to decrease.

Venereal Diseases in the Army and Air Force.—In *Nederlands militair geneeskundig tijdschrift* (9:54, 1956) Major H. B. van Haren reports that in the Army and Air Force in 1953 and 1954 there were only 208 new cases of venereal diseases (193 of gonorrhea, 5 of syphilis, 8 of veneral lymphogranuloma, and 2 of chancroid). In 1946 and 1947 about 4,200 fresh cases were observed. In view of the fact that the total Army strength increased by about 20% from 1947 to 1953, these figures are still more impressive. This decrease in the occurrence of venereal diseases among soldiers is proof of the diminution of these diseases among the total Dutch population.

UNITED KINGDOM

End of Colonial Medical Service.—As colonies become self-governing, many of the British medical officers employed by the governments of these territories are being relieved of their duties. This happened in India, and many physicians now serving in what may soon no longer be dependent colonies are anxious about their future. A white paper on the subject has been issued (Her Majesty's Overseas Civil Service: Statement of Policy Regarding Organization, London, Her Majesty's Stationery Office, 1956). This states that in territories where constitutional changes take place that fundamentally affect the condition of physicians serving the colony, compensation schemes will be negotiated with the governments concerned. In some areas, such as Nigeria, shortages of physicians and nurses are serious, and they are being urged to remain, particularly those with experience. They will be protected economically by being transferred to a special list in the Overseas Civil Service, and rates of pay and conditions of service will be laid down by the British government after consulting with the colonial authority. The former will pay pensions and any compensation payments if the physicians should be prematurely retired. At least a year's notice must be given before terminating employment, and all physicians affected must accept an obligation to serve the British government up to the age of 50

in any post to which they may be directed. The government hopes to find employment for all physicians affected up to the age of 50, up to which age pay will be guaranteed. If suitable employment cannot be found, the physician will be paid his pension and compensation. It is hoped to recruit physicians with exceptional administrative or professional qualifications to serve those colonial governments that are attaining self-government. The scheme has been criticized because physicians may have to retire from overseas service at 50, and no arrangements have been made for finding suitable employment for them in Great Britain.

Flour Contaminated with Insecticide.—At Pontardawe, Glamorgan, over 100 people have been affected in an outbreak of poisoning due to contamination of flour with Endrin, an insecticide. About 75 needed medical attention. Within one to three hours of eating bread made from the contaminated flour, the acutely ill patients became unconscious, those most severely affected suffering from epileptiform fits, sometimes accompanied by violent muscular contractions and a period of unconsciousness. Injuries to bones and joints were sustained in falling. Those with milder attacks suffered from weakness, nausea, twitching and tingling of the limbs, deafness, and mental confusion. All recovered without complications, except for injuries due to falling, but some remained ill for several days. Sixteen patients were hospitalized. Inquiries showed that 3 of 100 sacks of flour were contaminated. The flour at the bottom of the affected sacks had become saturated with a solution of Endrin in xylene. Live crops were not contaminated by spraying.

Epidemic Keratoconjunctivitis.—In November, an epidemic of keratoconjunctivitis occurred, which resulted in severe disability among workers in heavy industry on the river Clyde at Glasgow. In January the number of cases increased rapidly and a minor epidemic involved a large shipyard, from which it spread to other shipyards and factories. Complement-fixation tests with the adenoidal-pharyngeal-conjunctival—group virus antigen showed significantly rising titers in five of seven paired serum samples taken early and in the convalescent stages of the illness. Tests on 52 serums taken on the same day in cases of different duration, ranging from one to 112 days after onset, showed predominantly high titers after the 14th day, but low titers before the end of the second week. The findings point to a virus of the adenoidal-pharyngeal-conjunctival group as a cause of the outbreak. Attempts to isolate and identify the serologic type of virus have been unsuccessful, but investigations are proceeding.

New Cytostatic Drug.—Dr. Camillo Sellei and his co-workers in the *Lancet* of May 26 reported a clinical trial of a new cytostatic agent, B. C. M., formed by linking a nitrogen mustard with mannitol. It strongly inhibits the growth of metastasizing tumors and proliferating lymphocytes. The recommended dosage is 1.0 to 1.5 mg. per kilogram of body weight given intravenously on alternate days to a total of 900 to 1,000 mg. It can also be injected intrapleurally or intra-abdominally in isotonic sodium chloride solution. There is a risk of granulocytopenia with a total dose of more than 1,200 mg. Six of seven patients with chronic lymphocytic leukemia, three with chronic granulocytic leukemia, and two of four with acute leukemia showed great improvement, although this was only temporary. Lymphosarcoma was arrested in 3 of 5 patients, and, of 14 patients with Hodgkin's disease, excellent results in 6 and fair results in 4 were claimed. B. C. M. was given to 40 patients with cancer of the lung, and in 20 the pain was diminished and the general condition slightly improved. Two other patients with cancer were improved sufficiently to lead a nearly normal existence. B. C. M. is recommended specially for tumors of the lymphoid system.

Long-Term Treatment with Antibiotics.—Dr. James Livingstone and his co-workers reported their results with long-term use of oxytetracycline in a series of 38 patients with advanced chronic respiratory infections, one with chronic micrococcic bronchopneumonia, 17 with chronic bronchitis, 13 with infective asthma, and 7 with bronchiectasis (*Lancet* 1:775, 1956). Of these, 11 of the asthmatics were considered not to have a true infection, leaving 27 infected patients. A good early response was obtained in 24 of these, but for various reasons treatment was continued in only 14. Only eight were still receiving oxytetracycline, which had been given to some of them for two and one-half years. These were patients with chronic bronchitis and bronchiectasis, the original infecting organism in all being Hemophilus influenzae. They have shown great improvement. It was more difficult to obtain a satisfactory response if treatment was interrupted than if it was continued without a break. The benefit obtained was probably due not only to suppression of H. influenzae, but also to the prevention of recurrent acute pneumococcic infections. No pneumococci were isolated from the sputum while oxytetracycline was being given. Although the authors believe that deterioration will ultimately set in, owing to the development of resistant strains, this has not yet occurred in any patient who was treated without interruption. How long treatment can be continued is a matter of conjecture.

Artificial Oviduct.—Cross and Erskine have described the construction of an artificial oviduct, based on embryologic observations on the common origin of the peritoneum, oviduct, and ovary (*Lancet* 1:777, 1956). The procedure consists of making an opening in the uterus, lining this opening with peritoneum, and using the round ligament and local peritoneal tissue in fashioning the tube. This is constructed over a cord of polyethylene, which passes from the artificial aperture of the uterine cavity to the infundibulopelvic ligament near the ovaries. The polyethylene cord is left in place for 90 days, during which time the patient is given antibiotics.

Micrococcic Lung Infections.—Drs. Arthur and Myrddin Evans (*Lancet* 1:771, 1956) reported a series of 70 patients with micrococcic infections of the lungs. They made frequent bacteriological examinations of sputum and complement-fixation tests for evidence of infection with the viruses of influenza A and B, psittacosis, lymphogranuloma inguinale, Q fever, and lymphocytic choriomeningitis, as well as titrations of Streptococcus group MG agglutinins and heterophil antibodies. In four patients with influenza A infection, coagulase-positive Micrococcus pyogenes var. aureus was isolated from the sputum; two of these died. It was thought that the Micrococcus was a secondary invader. The fact that there was no detectable antibody to micrococcic α-hemolysis during the acute phase of the illness suggests that the circulating antibody had been neutralized by the toxin produced as a result of massive micrococcic infection.

The increasing incidence of micrococcic lung infections of infants was commented on by Disney and his co-workers in the same issue (page 767). Because they found that cultures made from the upper respiratory tract were generally uninformative, they cultured fluids obtained by thoracic puncture in selected cases. They claim that this procedure carries little or no risk. In infants with local signs of consolidation, thoracic puncture often yielded fluid containing coagulase-positive M. pyogenes var. aureus. Thirty-five cases of micrococcic pneumonia were diagnosed in 530 infants under 2 years of age admitted to the hospital with lower respiratory infections. Of these, 29 were primary micrococcic infections. Treatment consisted of alleviating anoxemia with oxygen and bringing the infection under control with penicillin or, in penicillin-resistant patients, with erythromycin.

Respiratory Virus Infection in the Royal Air Force.—During 1954-1955 Andrews and his co-workers made a survey of acute respiratory illness associated with viral infections in 10 Royal Air Force establishments in England (*Brit. M. J.* 1:1203, 1956). During the survey 1 in 14 of the men in the groups surveyed was hospitalized for more than 48 hours with a respiratory infection. Specimens of blood were taken from 1,001 patients, and influenza B virus was found in 134. Only 15 of these were sufficiently ill to require hospitalization. Six cases of influenza A infection were detected, but only two patients showed evidence of adenoidal-pharyngeal-conjunctival virus infection. In an acute febrile illness in seven boys' boarding schools, an outbreak of pharyngoconjunctival fever with enlargement of lymph nodes was observed. The clinical features were quite different from those of the adenoidal-pharyngeal-conjunctival group in the Royal Air Force. In two Royal Air Force units those who had a rising titer to influenza B virus were interviewed at the end of the investigation. About 33% had contracted typical influenza during the period, a third had minor respiratory symptoms, and the remaining third could not remember any illness.

In volunteers from five of the Royal Air Force establishments where well-defined outbreaks of influenza B occurred, evidence of a significant association was found between preepidemic levels of antibody to soluble antigen and subsequent susceptibility to infection.

Treatment of Breast Cancer by Irradiation of Pituitary.—Greening describes the treatment of advanced cancer of the breast by irradiation of the pituitary in *Lancet* (1:728, 1956). He stated that adrenalectomy, with a mortality rate of 6%, gives remission in only 35% of cases. Hypophysectomy, while giving a greater proportion of successes, has a similar mortality rate. An attempt was therefore made to destroy the pituitary gland by the implantation of unscreened radioactive gold (Au^{198}). Gold seeds were implanted in the anterior part of the gland through a small-bore needle introduced into the sella turcica, via the nose and sphenoidal sinus. Extremely accurate visual localization of the sella was obtained by means of an image intensifier working in two planes. During 18 months, 50 patients have been treated in this way with no deaths, no damage to the optic chiasma, no basal meningitis, and no rhinorrhea of cerebrospinal fluid. Irradiation of the hypophysis by Au^{198} appears to be a safe palliative measure in advanced carcinoma of the breast.

Rapid Test for Hepatolenticular Degeneration.—A rapid test for the early detection of hepatolenticular degeneration (Wilson's disease) is described by Ravin in *Lancet* (1:726, 1956). This is based on the finding that in this condition there is an abnormally low serum—copper oxidase activity. A simple, rapid, and accurate calorimetric estimation of this is used, requiring only standard laboratory equipment and depending on the presence of paraphenylene-diamine-oxidase in the serum. The activity of this compound is calculated from the absorption spectrum of serum and paraphenylene diamine incubated together for an hour.

Penicillin-Resistant Micrococci.—Micrococcic infections constitute a major clinical problem, particularly in hospitals, in which many of the strains are resistant to antibiotics, particularly penicillin. Fairbrother reported (*Lancet* 1:716, 1956) that, of 550 strains of Micrococcus pyogenes var. aureus recently isolated from infections, 57% were penicillin resistant. Previous figures for the same hospital were 42% in 1950-1951 and 57% in 1953-1954. An increase in penicillin-resistant infections throughout the community appears to be inevitable, particularly if the practice of using penicillin indiscriminately for all forms of trivial infection continues. A serious development is the great increase of severe infections caused by penicillin-resistant strains of M. pyogenes var. aureus, for which the use of penicillin is not only valueless but may also be dangerous because it delays the introduction of an effective antibiotic. A stricter control of penicillin therapy is suggested.

Pathogenic micrococci in primitive races are all sensitive to antibiotics. Dr. Phyllis Rountree examined nasal swabs from 120 natives of the Wabaga tribe in New Guinea, which has had practically no contact with white races (*Lancet* 1:719, 1956). Their existence was unknown until 1910. The area in which they live was not penetrated until 1934, and since that time no more than 30 white people have had contact with them. Twenty-three of the 120 natives were nasal carriers of M. pyogenes var. aureus, and none of the strains were resistant to penicillin, streptomycin, oxytetracycline, or chloramphenicol. Some of the nonpathogenic micrococci found in nasal swabs were resistant. Phage typing of the strains isolated from these primitive people showed that these were similar to those found in civilized man.

Help for Poliomyelitis Victims.—A party of five physiotherapists and one occupational therapist has left England for Buenos Aires to help in the aftercare of children and adults crippled by the poliomyelitis epidemic that swept Argentina last year. The Ministry of Health selected the volunteers after the Argentinian government had accepted the British government's offer to provide a team of specialists with particular experience in poliomyelitis and the use of respirator apparatus.

Parity and Diabetes.—In youth there is little difference in the sex incidence of diabetes, but after the age of 45 years the incidence is greater in women. Dr. D. Pyke has examined the effect of parity and weight in women on the incidence of diabetes (*Lancet* 1:818, 1956). Of 728 patients over 45, there were 477 women and 251 men. The percentage of diabetics in parous women rose with parity. The incidence was no greater in the nulliparous than in the general female population of the same age, and it was only slightly greater in primiparas. It rose with each succeeding pregnancy, being 171% greater than the expected value in women who had three children and 300% greater in those who had five children. Thus, a woman who has five children appears to have about three times as great a chance of developing diabetes as a woman who has had none. Parity, however, did not lead to the appearance of diabetes earlier in life; the age at diagnosis was similar for all degrees of parity and was about 60 years. The effect of parity was not due merely to a slightly greater tendency of multiparas to become fat, since the preponderance of women diabetics is found among those who are of normal or below normal weight. The menopause is unlikely to be an important causal factor because, if it were, an excess of women diabetics would be expected in all parity groups who reached the climacteric, whereas this is not the case.

Enuresis.—Blomfield and Douglas (*Lancet* 1:850, 1956) collected data on the incidence of enuresis among 4,294 children (2,268 boys and 2,026 girls). At 6 years, 1.8% of the boys and 4.1% of the girls were enuretic by day; 12.2% of all children were enuretic at night; and by the age of 7 years and 9 months the proportion had dropped to 7.3%. At each age fewer girls than boys were enuretic at night, and among those severely affected, the difference between the sexes increased with increasing age. Assuming these figures are true for the country as a whole, the authors calculate that among children aged 4 years in Great Britain 80,000 are occasionally and 30,000 regularly enuretic at night; the figures at 7 years are 30,000 and 20,000. Comparison of different social groups suggested that enuresis in between 33 and 50% of the children could be prevented by a change in upbringing and environment. There are great social differences in the time that toilet training is started and control achieved. The poorest families start training latest and their children are latest in achieving control. In each social group early training was associated with a low prevalence and late training with a high prevalence of enuresis. At least part of the social difference recorded was considered to be the result of different patterns of training, but only part, because in the children of agricultural workers toilet training starts late, and the prevalence of enuresis is low. There was no significant difference in enuresis between first-born and later-born children.

Triac.—Triac, the acetic acid analog of triiodothyronine, has an immediate thyroxin-like action. Trotter (*Lancet* 1:885, 1956) found that in patients with myxedema it has a relatively greater effect than thyroxin in lowering the blood cholesterol level but has only about 1.3% the activity of triiodothyronine in this respect and in raising the basal metabolic rate. In euthyroid subjects with coronary artery disease, Triac lowered the cholesterol level without materially changing the metabolic rate. A dose of about 3 mg. daily lowered the cholesterol level by about 25%. In three patients whose dose of Triac was increased gradually to 4 mg. daily, there was no obvious rise in the basal metabolic rates although the cholesterol level fell. These preliminary observations suggest that a detailed comparison of the effects of thyronine derivatives on blood lipids would be worth undertaking. Triac also reduced the uptake of radioactive iodine by euthyroid patients, the dose required being about 25 times greater than that of triiodothyronine.

Ulcerative Colitis.—Truelove and Richards examined over 100 biopsy specimens of the colonic mucosa from just above the rectosigmoid junction from patients with ulcerative colitis (*Brit. M. J.* 1:1315, 1956). The biopsy was harmless, as there was no local bleeding or infection and there were no bad effects on the course of the disease. The specimens, which measured 0.4 cm. in diameter, were obtained at 6 to 8 in. from the anus. A group of 24 patients subjected to sigmoidoscopy but without lesions of the colon were studied as controls. Biopsy specimens of colonic mucosa were normal in all but two of them. These showed increased proliferative activity in the epithelium. Of 71 specimens taken from patients with ulcerative colitis with symptoms, 67 showed inflammatory changes. The glandular tubules were irregularly arranged and often showed increased prolifera-

tive activity, edema, congestion, interstitial hemorrhage, an increase in infiltration by lymphocytes, plasma cells, eosinophils, neutrophils, and inflammatory exudate. Breaches in the epithelium were common, and both glandular and necrotic cells were shed into the glandular lumens. In severe cases there were crypt abscesses. More than half of 40 specimens taken from patients in clinical remission showed inflammatory changes. The sigmoidoscopic findings failed to correlate with the clinical state in one major respect—more than half the patients in clinical remission showed sigmoidoscopic evidence of disease. In a third of the patients with normal sigmoidoscopic findings, the biopsy specimens showed some degree of inflammation. Although the diagnostic value of sigmoidal biopsy is doubtful, the changes in histological appearances in an established case can be correlated with the clinical course of the disease. This was proved by repeatedly taking biopsy specimens during periods of remission and exacerbation. The authors believe that crypt abscesses play an important role in ulceration.

Poliomyelitis in the Tropics.—Although poliomyelitis is rare in native tropical populations, virtually all members of which are immune after the age of 5 years, an outbreak in the Nzega district of Tanganyika, with a population of 200,000, is reported by Kerr and Pease (*Brit. M. J.* 1:1337, 1956). The incidence was 99 paralytic cases per 100,000, and 95 of these were in persons under age 5. The epidemic was severe, and it occurred in a primitive community. The outbreak was attributed to a virulent strain antigenically similar to the relatively avirulent strain or strains that had apparently immunized most persons over the age of 5 years. While its source is unknown, it was probably introduced from outside, although it may have resulted from the activation of a dormant strain or from a natural mutation of strains already present. The authors conclude that outbreaks in primitive peoples must be expected with increasing frequency, unless a vaccine can be produced in sufficiently large quantities to immunize them.

Poisoning from Ethylene Glycol.—A death due to drinking an antifreeze mixture containing ethylene glycol is reported by Dr. I. Ross in the *British Medical Journal* (1:1340, 1956). A man drank 150 to 300 cc. of antifreeze. Five hours later he appeared ill and drowsy, and the next day he went into a coma. About 24 hours after taking the antifreeze he became delirious, his temperature and blood pressure rose, and lumbar puncture showed a turbid spinal fluid. A day later twitching of the arms and face occurred, the limb reflexes were brisk, the abdominal reflexes were absent, plantar responses were extensor, the liver was enlarged, and the patient was anuric. There were signs of a chemical meningoencephalitis. The blood urea level rose to 330 mg. per 100 ml. The blood pressure, which was 110/70 mm. Hg on admission to the hospital, rose to 200/115 mm. Hg. Twelve days after taking the antifreeze the patient died. At autopsy the kidneys were enlarged and showed hydropic degeneration, the lungs exhibited bronchopneumonic consolidation, and the right side of the heart was dilated. Death was attributed to acute cardiac and renal failure.

Is Dimethyl Phthalate a Drug?—The National Health Service Regulations provide that when a physician in the service prescribes preparations that are not considered to be drugs, the cost of the preparations may be recovered from him. A recent case in point concerns dimethyl phthalate, an insect repellent, which a physician prescribed for a patient who had once had malaria and was traveling to a malarial zone for a week. The executive council decided that dimethyl phthalate was not a drug. The physician appealed to the local medical committee, which decided it was a drug. Because of the disagreement of opinion the Minister of Health put the matter before referees. At the inquiry the physician justified his prescription of the repellent as an agent for the prophylaxis of malaria and put it in a class of other preventative measures, such as revaccination against smallpox or typhoid fever. The counsel for the Minister of Health argued that a mosquito repellent was not a medicine, because its action was external. He compared it with a mosquito net or a beekeeper's veil. The referees stated that, if dimethyl phthalate were considered a drug, there was no reason why housewives should not be provided with a spray to keep off flies. They decided that dimethyl phthalate was not a drug that the health service was called on to provide.

Rehabilitation.—In *Rehabilitation* (Spring, 1956, page 2) Richardson and Weir analyze the findings in 84 disabled patients who have been followed for six months. Their major conclusion is that age, skill, and motivation to work are more important than disability in determining successful rehabilitation. Thus, while at the end of six months 47.6% of the entire group were employed, the under-40's contributed 70% of the employed group and only 52.25% of the unemployed group. The severity of disability was similar in both the employed and the unemployed, irrespective of age. Within each grade of skill the proportion of employed was higher in the younger age group, and in both age groups the proportion of employed was least in the unskilled. Further, whereas 60% of the employed had an I. Q. above 100, the corresponding figure in those not unemployed was 43%. Motivation is the most important single factor. Given a positive attitude the prospect of placement is greatly enhanced, but there is still too great a tendency to attribute success or failure to the degree of physical handicap. Family influences are a powerful factor in motivation or the lack of it.

Nuclear Radiation Hazards.—The report of the Medical Research Council committee, appointed last year to investigate the hazards to man of nuclear and allied radiations, in considering the possible genetic effects, uses as a standard the "doubling dose" or quantity of radiation required to double the spontaneous mutation rate. This dose almost certainly lies above 3 r, but it may even be more than 150 r. Representative values probably lie between 30 and 80 r. It is extremely improbable that in times of peace the whole population, or a large fraction of it, will receive an additional dose of this magnitude from industrial or other sources. Even in the case of the small number who may be employed on certain industrial processes or be receiving medical treatment involving x-rays, no noticeable effects will be produced either on their immediate offspring or their descendants. For levels up to doubling dose, and even some far beyond, the genetic effects of radiation are appreciable only when reckoned over the population as a whole and need cause no alarm to the individual on his own account.

Diagnostic radiology is the most important source of man-made irradiation. In 1955 nearly 18 million x-ray examinations were carried out in England and Wales, and it is estimated that the amount of radiation reaching the gonads from this source is as much as 22% of that derived from natural sources. The total dose to the gonads from natural sources is estimated to be 0.1 r per annum, or 3 r per generation of 30 years. The contribution from radiotherapy is much less than that from diagnostic radiology, but probably greater than that from any other source. X-ray fluoroscopy for shoe fitting contributes not more than 0.1% of the dose to the gonads received from natural radiation. The average luminous wrist watch contains about 0.2 μc of radium, and the calculated dose to the gonads from wearing such a watch is about 0.01 r a year. As there are in use in this country about 3 million men's watches, one million women's and children's watches, and 10 million luminous alarm clocks, it is estimated that the population dose from this source is about 1% of the natural background. The population dose from television sets is estimated at much less than 1% of the dose received from natural radiation. The amount of radiation from cosmic sources is greater at high altitudes, but it is estimated that the additional dose received by persons in aircraft, averaged over the whole population, is at present insignificant compared with that received from the natural background.

For the 9,000 medical workers and 5,000 industrial workers occupationally exposed to irradiation, it is estimated that the average gonad dose per person is about 2.5 r a year, and that this constitutes 1.6% of natural background radiation. The Atomic Energy Authority now employs about 7,000 people, and the average dose these receive from all occupational sources of radiation is 0.4 r a year. It is estimated that the gonad dose averaged over the population as a whole is about 0.1% of the natural background.

From the nuclear devices exploded in other parts of the world up to the present time, the population of this country may expect to receive over the next 50 years additional radiation amounting to 0.02 to 0.04% of the radiation that will be received over the same period from natural sources. If the firing of bombs were to continue indefinitely at the same rate as over the past few years, radioactivity would gradually accumulate to a level at which an inhabitant of this country would receive an average

dose of 0.026 r over a period of 30 years, or about 1% of that which he would receive in the same period from natural sources. The contribution to this figure of thermonuclear explosions, relative to their numbers, is very great. If the rate of firing of weapons of this type increases, exposure to radiation will be significantly increased. It is unlikely that the inhalation of radioactive particles present in the air as a result of fall-out would constitute a problem in ordinary life. The deposition of radioactive strontium is probably a greater hazard, as it is soluble and, if ingested, is deposited and retained in bone. Measurements that have been made of radiostrontium in bone show that the highest levels are at present about 1,000 times less than is considered permissible for those who are occupationally exposed. Calculation of the fall-out likely to come, if the present rate of firing continues, suggests that this level may be increased tenfold in the course of several decades. The present level would produce no detectable increase in the incidence of ill-effects, but we are now accumulating radiostrontium at an appreciable rate and a close watch will need to be kept on the increase. The possibility cannot be ignored that, if the rate of firing increases, and particularly if greater numbers of thermonuclear weapons are used, we could within the lifetime of some now living be approaching levels at which ill-effects might be produced in a small number of the population. The time has come for a review of present practice in diagnostic radiology and of certain uses of radiation in the treatment of nonmalignant conditions, particularly in children. Among the less important sources of radiation, it is hoped that the use of x-rays in shoe fitting will be abandoned except when prescribed for orthopedic reasons; that watches and clocks with luminous dials will be confined to necessary uses; and that the x-ray hazard from television tubes, at present negligible, will be borne in mind if special types of high voltage equipment come to be widely used.

As an appendix to the report, the findings in an investigation into 13,352 patients with ankylosing spondylitis who had been treated with x-rays at 81 radiotherapy centers during the period 1935 to 1954 inclusive are given. These patients had all been followed for periods ranging from one year to 20 years, with an average for the group of just under 5 years. Of the entire series, leukemia, aplastic anemia, or myelofibrosis had developed in 49, and 46 of them had died by the end of 1955, 28 from leukemia, 13 from aplastic anemia, and one from myelofibrosis. Three other patients with leukemia and one with aplastic anemia had died from other causes. The numbers of deaths from leukemia and aplastic anemia that would be expected under normal conditions were 2.9 and 0.3 respectively. The differences between the observed and expected deaths from both diseases are highly significant. This increase is believed to be the result of exposure to x-rays, although the possibility that patients with ankylosing spondylitis are unusually sensitive to the action of x-rays cannot be excluded.

Reciprocity with Sweden.—The United Kingdom and Sweden have concluded an agreement on social security whereby British families will qualify for Swedish family allowances as soon as they become civilly registered in Sweden and British nationals resident in the United Kingdom will be entitled to use the Swedish health services while they are in Sweden. Sweden is the first country outside the Commonwealth to offer full reciprocity with the British Health Services by making its health services available for all British nationals, including tourists. Agreements with other countries have covered only British nationals employed in those countries. The agreement also covers the cash benefits provided by the two countries for unemployment, sickness, maternity, old age, widowhood, orphanhood, and industrial injury. The agreement will not come into force until it has been ratified.

William Harvey Tercentenary.—June 1957 marks the tercentenary of the death of William Harvey. The Harveian Society of London proposes to commemorate the occasion by holding an international scientific symposium on the circulation, June 3 to 7, 1957, in the Royal College of Surgeons. The subjects to be discussed include: "The Circulation from the 17th to the 20th Centuries," "Regulation of the Circulation," "Results of Cardiac Surgery," "Coronary Circulation," "Pulmonary Circulation," "Cerebral Circulation," "Splanchnic Circulation," and "Peripheral Circulation." The concluding meeting will be held at Folkestone, Harvey's birthplace.

Antenatal Care and Toxemia.—Although the maternal mortality rate in England and Wales is now under 1 per 1,000, there are still over 500 maternal deaths annually, many of which are preventable provided antenatal supervision is adequate. Toxemia of pregnancy is the principal cause of avoidable maternal deaths, and the early recognition of toxemia depends on an antenatal routine designed to detect a slight rise in blood pressure, slight edema, or unduly rapid gain in weight. Albuminuria is a late sign, indicating a serious risk of antepartum hemorrhage.

In its recommendations the Standing Maternity and Midwifery Committee of the Ministry of Health stresses the importance of the patient's personal history. Any evidences of malnutrition, renal disease, heart disease, pulmonary tuberculosis in the past, or complications in a previous pregnancy are reasons for delivery in the hospital. All primiparas over 30 years old, all multiparas over 40, mothers who have had three or more previous confinements, and those with multiple pregnancies should have their confinements in hospital. The first examination should include an x-ray of the chest, a full dental examination (with any treatment required), and examination of the blood to determine hemoglobin value, blood group, and Rh status and for evidences of venereal disease. The hemoglobin determination or even a complete blood examination should be repeated at 30 to 32 weeks. An appreciable number of maternal deaths from ante or postpartum hemorrhage could be prevented if preexisting anemia were detected and then treated. Supplemental iron is required by about 25% of expectant mothers and should be given if the hemoglobin level is below 80%. The importance of the Rh examination is shown by the fact that deaths of infants due to hemolytic disease rose from 410 in 1953 to 461 in 1954. It is recommended that the physician see the mother again at 30 to 32 weeks and 36 weeks and that in the interval she be examined by the midwife monthly until the 28th week, fortnightly until the 34th or 36th week, and then weekly.

Care of Epileptics.—Although precise figures are not available, the incidence of epilepsy in this country is probably about 4 per 1,000 of the population, according to a report (The Care of Epileptics) published by a subcommittee of the Standing Medical Advisory Committee of the Ministry of Health. About 10% of all epileptics have antisocial behavior disorders. At present there are two hospitals in the National Health Service that provide special care for epileptics. In addition there are eight epileptic colonies and homes, six run by voluntary bodies and two by local authorities. The present position with regard to the care of epileptics is unsatisfactory, in that a few patients receive no treatment for their epilepsy, while others are merely taking routine doses of various drugs, which may have been first prescribed long ago and never reviewed. The major recommendation of the committee is that, although the general practitioner should continue to be responsible for the long-term medical supervision of the epileptics in his practice, each regional hospital board should establish a diagnostic and treatment clinic for each million of its population and a long-term treatment and rehabilitation center for each 2 million of its population. These clinics and centers should normally be under the direct supervision of a neurologist, who is the leader of a team consisting of pediatricians, psychiatrists, child guidance experts, radiologists, almoners, psychologists, and others. Electroencephalographic facilities and the services of a neurosurgeon should also be available. Special attention should be devoted to the care of epileptics with behavior problems, many of whom are suffering from temporal lobe epilepsy, a condition in the treatment of which surgery may play an important role.

Whenever possible, children suffering from epilepsy should be educated in ordinary schools. A plea is made for the greatest care in the labeling of children as epileptics. Some children who have not had a fit for many years have continued to be regarded as epileptics. If a child remains free from fits after treatment has been withdrawn for a certain time, he should certainly not be regarded as suffering from epilepsy, although he should continue under such medical supervision as may be deemed necessary. The patient whose main disability is a mental defect but who has occasional fits should enter a mental hospital, not an epileptic colony. The aggressive antisocial epileptic should be classed as a psychopathic personality rather than as primarily epileptic. Experience shows that the patient suffering from both psychopathy and epilepsy often has disease of, or damage to the brain. In the case of the younger patients operation may offer hope of ameliorating, or removing, both types of symptoms

MISCELLANY

LABORATORY DIAGNOSIS OF POLIOMYELITIS AND POLIOMYELITIS-LIKE DISEASES

Relatively recent findings that indicate that many diseases masquerade as poliomyelitis have made physicians increasingly aware of the difficulty of diagnosing true poliomyelitis. It is now generally recognized that nonparalytic cases cannot be accurately diagnosed without laboratory tests. There is growing evidence that laboratory tests are equally important in diagnosing some paralytic cases. Agents that may produce a clinical picture similar to poliomyelitis include, in addition to ECHO and Coxsackie types of virus, such infections as lymphocytic choriomeningitis, mumps, and herpes.

The development of the poliomyelitis vaccine intensifies the need for laboratory confirmation of all cases of poliomyelitis and poliomyelitis-like diseases. With widespread vaccination, the incidence of true poliomyelitis can be expected to decrease, and it will be more and more difficult to identify clinically the isolated and sporadic cases that do occur. Moreover, the vaccine itself may modify the course of the disease, thus further complicating the diagnostic problem. If an accurate evaluation is to be made of the total and long-range effect of the vaccine, it is essential to confirm all reported cases by laboratory testing.

To provide such confirmation, a network of laboratories, especially equipped to analyze specimens taken from patients with poliomyelitis or poliomyelitis-like diseases, has been organized by the Communicable Disease Center of the Bureau of State Services, Public Health Service, U. S. Department of Health, Education, and Welfare. The network includes a number of academic research laboratories and state health department laboratories. Physicians are urged to use these facilities, sending specimens to their state health department or to whatever laboratory is designated by their state health department. Full cooperation by all physicians will both promote research and make possible a definitive evaluation of the effectiveness of the poliomyelitis vaccine. In collecting, preparing, and shipping specimens, the procedures outlined below should be carefully followed.

Preparation and Shipment of Diagnostic Specimens

Type of Specimen to Be Collected:

Virus Isolation.—Materials for isolation must be freshly obtained. Feces have been the most productive medium, and that obtained from normally passed stool or fecal material collected by glove or swab is suitable. Throat washings or swabs and spinal fluids may also yield agents. Since the likelihood of isolating virus is increased by collecting several specimens over a period of time, it may be desirable, where circumstances permit, to collect additional specimens separated by 48-hour intervals.

Serologic Tests.—Serum is to be obtained from clotted blood collected and kept under sterile conditions. No preservative need be added. Serum separated from clot at source prevents hemolysis, which interferes with some tests. If it is not possible to separate the serum from clotted blood, whole blood can be used. However, whole blood must be shipped promptly so that it reaches the laboratory within 24 to 48 hours after it is collected. At least 20 ml. of blood (10 ml. of serum) should be collected for serologic examination to permit a multiplicity of tests, confirmation, or repetition of tests when equivocal results make this necessary.

Time to Collect Specimens:

Virus Isolation.—The time in the course of the clinical disease that specimens are collected is of utmost importance. In general, the earlier in the acute stage the specimen is taken, the better the chance for successful isolation of the virus. Certainly, the specimen should be taken while the patient is still acutely ill and febrile. Several serial specimens, each separated by a day or more, may improve chances of isolation.

Serologic Tests.—Serum specimens *must be paired,* since significance can only be attached to an appreciable *rise* in antibody titer. The first sample should be collected as early in the illness as possible and the second from two to eight weeks after the beginning of convalescence. The best method is to take a series of samples: acute, two, four, and eight week convalescent.

Container for Specimen:

Virus Isolation.—Specimens should be placed in bottles or jars with tight stoppers, or in tubes with rubber stoppers, and secured with tape. Unless they can be shipped to reach the laboratory within 24 hours of the time they are taken, they should be frozen as soon as they are collected and kept at a temperature of −10 C or lower.

Serologic Tests.—The type of container must protect the serum or blood from loss by breakage as well as from contamination and deterioration. Samples in test tubes with tight rubber stoppers (reinforced by adhesive tape) or leakproof screw-top vials are satisfactory.

Packing and Shipping Specimens:

Virus Isolation.—Frozen specimens (i. e., all specimens except those that can reach the laboratory within 24 hours after collection) should be packed in dry ice and shipped in an insulated carton by the most rapid means available. Unfrozen material need not be shipped under refrigeration but should be carefully packed to avoid breakage. It is particularly important that specimens that are not frozen reach their destination rapidly, as delay reduces the chances of recovery of virus.

Serologic Tests.—Serum samples for serologic tests may be shipped without refrigeration in ordinary mailing containers, adequately protected against spillage and breakage. However, these specimens should also be sent by the most rapid method.

Data to Be Supplied with Specimens:

The Polio Surveillance Program.—Specimen Shipment Form [PHS 400.119 (CDC) Ga.], available from the state health department laboratory or epidemiology service, lists the information desired on each patient. Briefly, this requests identity and

---

This report is from the Bureau of State Services, Public Health Service, Department of Health, Education, and Welfare.

brief personal history of the patient with date of onset, clinical impression, antipoliomyelitis vaccination history, indication of contact with similar cases, and type of material collected and dates collected. Specimens should be forwarded as directed by the state public health laboratory. Results will be reported to the physician. While the laboratory tests have been simplified, and the procedure shortened substantially, the results of laboratory examination may not always be of value with respect to a specific patient. In some cases, however, they may be of immediate use, and in all situations where adequate information is obtained the results will have epidemiological significance (see figure).

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service — Communicable Disease Center

POLIOMYELITIS SURVEILLANCE PROGRAM

Specimen Shipment Form

To be filled in by laboratory:
Date received_____ Lab. No._____

Type of specimen(s):

Item	Date Coll.	Date Sent
Stool 1		
2		
Rectal Swab 1		
2		
Throat Swab		
Blood		
1. Acute		
2. Convalescent		
3. Convalescent		
Autopsy Specimen(s) (specify)		
1.		
2.		
3.		
4.		

Specimen(s) collected from:

1. Name_____ 2. Sex___ 3. Age___

4. State_____ 5. County_____ 6. City_____

7. Street Address_____

8. Date of first symptoms_____

9. Vaccination (check appropriate item):
___1955 ___1954 ___None

10. Clinical diagnosis (check appropriate item):
(a)___Fatal (b)___Bulbar (c)___Paralytic
(d)___Non-paralytic (e)___Suspect (f)___Not ill
(g)Other_____
(specify disease)

Specimen(s) collected and sent by:

Name_____

Title_____

Address_____

11. Contact of polio case: _____Yes _____No

12. Other pertinent information:

(If you desire acknowledgement of receipt of specimen(s), please insert your name and address in the box provided below.)

To be filled in by laboratory:

Laboratory Specimen No.	Type of Specimen	Date of Receipt	Condition of Specimen	Name of Patient

Sender's Name and Address:

Receiving Laboratory:

_____

Signature_____

THE LEISURE CORNER

SKIN DIVING

Devotees of the sport claim that skin diving is the fastest growing hobby in the world today. Nowhere is it so popular as in the United States, where nearly 2 million persons are enthusiastic about its fascinations. Many persons find themselves committed to the sea the moment they put on masks and snorkels. Brushing fins with some of the inhabitants of the sea, skin divers often develop so great a love for the sport that they give it every leisure moment they can. It is a hobby that can be practiced and enjoyed in all clear, unpolluted waters—inland rivers, lakes, and the sea.

An athletic generation of doctors now participates in the thrilling pursuit of fish, which is very much a part of skin diving. Having discovered that there is far more to life under water than just the thrill of harpooning a prize of the deep, they have had revealed to them the complete release that comes with moving about in a veritable "liquid world." The joy and stimulation derived from underwater movement tempts every skin diver to pursue the enchanting beauty found in the sea. Actually the sea unfolds a new frontier fully capable of capturing the scientific imagination of any doctor who wishes to invade a world three times as large as the one in which we live.

Modern diving equipment enables the skin diver to adapt himself with reasonable security and comfort to an element once reserved entirely for fish. Since the introduction of the terms "skin diving" and "spear fishing" into the vocabulary of sportsmen, methods and equipment employed in these underwater activities have undergone a series of developments. The matter of wearing masks, fins, and guns started on a large scale in the Mediterranean. Although the technique of modern-day skin diving has been greatly influenced by Italian and French divers of a generation ago, many Americans residing in Florida and California have added new tricks to the skin diving technique. From 1945 to the present, the perfection and volume of equipment manufactured in the United States and in Europe have been phenomenal. The sale of these articles in the United States alone has been running well over 50 million dollars for the past three years. At this point it is just as well to note parenthetically that while mask, snorkel, and fins give a skin diver unknown flexibiliy in water, they are completely dependent on the wearer's proficiency in swimming. Possession of a good water technique as well as a fairly good physical condition are necessary attributes for underwater sports, whether spear fishing or skin diving.

For the doctor who is about to start spear fishing activity, essential equipment consists of a mask, snorkel, fins, and a gun. First and foremost, the face mask makes it possible for the diver to see clearly under water. A mask provides the skin diver with a glass-framed picture of constantly changing beauty of a world under the sea. Face masks, equipped with shatterproof glass, are considered more practical than those provided with plastic lenses, since they have less tendency to scratch and fog on the inside. The head straps of a mask are adjusted to fit snugly; the edges of the mask coming in contact with the skin of the face should be soft and flexible so as not to pinch or chafe. Once a mask is comfortably in place, the wearer tries to breathe through his nose in order to check if it is airtight. If air enters through cracks, it follows that water will too. Testing a mask in shallow water facilitates necessary adjustments and at the same time permits the diver to practice mouth breathing and to habituate himself to his mask-encased nose.

The word snorkel is derived from the name of the apparatus used by German submarines, at the end of World War II, that allowed them to run just below the surface of the sea while drawing fresh air into the hulls. Equipped with a snorkel, a skin diver has only to swim leisurely on top of the water, breathing easily and comfortably, watching the bottom of the water with undivided attention through the clear glass of his face mask. Fins or flippers, which are worn on the feet, provide anywhere from 30 to 40% more propulsion to the diver. Fins should be fairly stiff and not too flexible in order to get the best results from one's footwork. At first, these new extensions of the feet tend to tire the swimmer, since sets of muscles are newly brought into play. Novice skin divers usually have annoying muscle strains and painful cramps in the legs. The flutter kick, which is used in the crawl stroke, provides the best results with the least effort on the part of the swimmer. A slow rhythmic kick gets one about with surprisingly little work and conserves a lot of energy. When spear fishing first loomed on the horizon, the sports diver learned to use a simple hand spear. Today dozens of different model guns can be purchased. Starting with the simple Hawaiian sling gun, the forms now available include guns powered by rubber bands, metal springs, compressed air, and carbon dioxide. Some are quite formidable and dangerous, and all should be handled with the respect that is due a dangerous weapon. No matter how well equipped a diver is, success in spear fishing really depends on the diver himself. Spear fishing requires considerable skill and patience, a good amount of second wind, and fairly well conditioned reflexes.

To the diver more interested in exploring the deeper parts of coastal waters than in hunting down its fishy inhabitants, air lungs are available at prices ranging from $70 to $200. The principle on which all air lungs are based is essentially the same. Most lungs use the original Cousteau-Cagnan feature, which has the air line entering the mouth directly, where it is held in place by the teeth. The lung developed by the Scott Aviation Company uses a full face mask, which covers both the nose and the mouth, allowing both structures to be utilized in breathing under water. Diving lungs are designed to be slightly buoyant, following Archimedes' principle: a solid body immersed in a liquid is buoyed up by a force equal to the weight of the liquid displaced. The doctor who undertakes to learn these techniques need not be reminded that deaths from air embolism have occurred when skin divers surfaced too quickly even from depths of less than 10 m. (32.8 ft.). The adjustment of buoyancy by using weight belts also introduces an element of danger. A few sessions with a good instructor are well rewarded.

The time a skin diver will spend under water, no matter how short a period, will often result in some bit of acquired information about marine life. Much of our information about the sea has come from such sources as ships' logs, fishermen's reports, and even native legends. Now that the sea is wide open to sportsmen, many physicians will enjoy directing their scientific training to the marine world, breaking the barrier of mystery and isolation that the sea has maintained for thousands of centuries. Improvements in underwater photography during the past few years have encouraged many skin divers to abandon the harpoon and take up the camera instead. Today camera-equipped divers are taking thousands of pictures of undersea life. A photograph provides a sure and efficient method for capturing a multitude of detail for later study in classroom and laboratory. No matter how eloquent a diver may be with word or pen, he can seldom hope to transmit the fleeting vividness of a particular moment with the same precision and clarity as that provided by a few good photographs.

A diver who is equipped with two cylinders of air can remain under water at a depth of about 30.5 m. (100 ft.) from 12 to 20 minutes and still be able to manipulate his camera with ease. The development of underwater photography was begun in 1893 by a French biologist named Dr. Louis Boutan. He made recognizable pictures under water with what would seem today to be the most primitive mechanism: a fixed-focus camera enclosed in a huge box consisting of copper. At the turn of the century Dr. Boutan made the first underwater night pictures, with light emanating from burning magnesium encased in a diving bell apparatus. Since the end of World War II underwater photographic equipment has been greatly perfected. As a result, knowledge of underwater photographic conditions has also improved and broadened. The Cousteau Undersea Research group, which has extensively covered the underwater field in pictures and books, is currently photographing the excavation of a 2,000-year-old galley in 42.6 m. (140 ft.) of water for a motion picture soon to be released.

There is a modern canyon below the world we live in, full of dark green weeds, black sea urchins, and small flower-like white algae. Fingerlings glide in the clear blue infinity down into which the sands slope. If you ever want the experience of flying without wings, standing up-side-down on one finger, doing somersaults, and playing hide-and-seek with fish, all these thrills can be yours when you go skin diving—and the inhabitants that you will meet in this wonderland of the sea will never discuss medicine with you.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Complications of Myocardial Infarction. C. A. Laugach Jr. Pennsylvania M. J. 59:673-676 (June) 1956 [Harrisburg, Pa.].

Relatively few patients with myocardial infarction die at the onset of their illness, and the survival of the others is greatly influenced by the management of the resulting complications. Shock should be recognized when signs of peripheral vascular collapse are present as well as hypotension. Some patients may have hypotension associated with left ventricular failure. If an attempt is made in these patients to raise the blood pressure by intravascular infusion or the use of a pressor agent, the left ventricular load may be sufficiently increased to cause pulmonary edema. Vasopressor drugs are more likely to help those patients who have normal or relatively low peripheral resistance. Unfortunately, there is no simple test for determining the peripheral resistance. Therefore, the response of the peripheral circulation to the judicious administration of a pressor agent may serve as a clinical guide.

The persistence of pain in acute myocardial infarction may indicate persistent myocardial ischemia and progressive myocardial necrosis. Many of the patients with persistent pain do not survive. The administration of oxygen in addition to narcotics will frequently give relief to these patients. The administration of bishydroxycoumarin (Dicumarol) also frequently relieves pain. Premature ventricular beats are the most common of the arrhythmias complicating myocardial infarction. When they are numerous, they may be a premonitory sign of ventricular tachycardia or a fatal episode of ventricular fibrillation. Quinidine or procaine amide (Pronestyl) are usually effective in suppressing these premature beats. The value of quinidine in preventing the more serious ventricular arrhythmias and sudden death is debatable. The second most frequently noted arrhythmia is atrial fibrillation, which usually subsides spontaneously.

Acute left ventricular failure or congestive heart failure may develop shortly after the onset of acute myocardial infarction. Acute left ventricular failure is the more common and it often appears earlier in the course of the illness. Early treatment with sedation, oxygen, and digitalis may prevent its progression to fatal pulmonary edema. Congestive heart failure should be treated like congestive failure in any other situation. The development of phlebothrombosis in the extremities is frequently insidious. While the use of anticoagulants has proved valuable in the prevention of these thromboembolic accidents, there is no agreement on the routine use of these drugs.

Rupture of the heart is an infrequent complication. It usually occurs during the first two weeks, while there is maximal myocardial necrosis. When the free wall of the left ventricle is involved, there is usually sudden death. Rupture of a papillary muscle results in the sudden onset of free mitral regurgitation and left ventricular failure, with survival usually a matter of hours. Perforation of the interventricular septum is also manifested by the sudden onset of left ventricular failure, but survival is longer. That physical activity may play a part in rupture of the heart was revealed by a study of a group of psychotic patients with acute myocardial infarctions whose activity could not be controlled. An increased incidence of rupture of the heart after acute myocardial infarction has been noted when there is persistent hypertension. The author also comments on the relation of ventricular aneurysm to thromboembolism and rupture of the heart. A small number of patients with myocardial infarction (15%) will have shoulder pain with limitation of motion in the affected joint. The pain may radiate into the arm and chest. Encouraging the patient to use his arms during convalescence may prevent the development of a frozen shoulder. The use of an analgesic agent and mild exercise may be all the active treatment needed once the complication has presented itself.

Thrombocytopenic Purpura Due to Quinidine: I. Clinical Studies. F. G. Bolton and W. Dameshek. Blood 11:527-547 (June) 1956 [Baltimore].

Thrombocytopenic purpura as a result of hypersensitivity to chemical substances is relatively uncommon. It occurs after exposure to organic arsenicals or sedormid or other drugs such as quinidine. Data obtained in five cases clearly indicated that the thrombocytopenic purpura from which the patients were suffering was due to sensitivity to quinidine sulfate and that quinidine is able to cause agglutination of platelets in a normal platelet-rich plasma (serum). Sometimes an antibody is present, a potential platelet-destroying mechanism. Quinidine intoxication occurs most commonly in women over 50 years of age who have been given quinidine after an attack of palpitation. The toxic effects are of two main types: those due to overdosage, which may occur after quite small doses and which may lead to "cinchonism" (tinnitus and other auditory disturbances; blurred vision and other ocular symptoms; nausea; and diarrhea) and those due to abnormal reactions or drug allergies (drug hypersensitivity), which are frequently those of allergic diseases: skin rashes, serum sickness, arthritic drug fever, asthma, lymphadenopathy, arthralgia, agranulocyosis, rarely hepatic damage, and thrombocytopenic purpura, any or all of which may follow the use of quinidine with or without another drug; they disappear suddenly when the drug is withdrawn. In some cases intoxication by quinidine resembles an East African disease of unknown origin called "onyalai."

Subacute Alcoholic Noncirrhogenous Hepatitis: Histobiological Types. G. A. Albot, C. Schlumberger, C. M. Faye and others. Semaine Hôp. Paris 32:1705-1722 (May 20) 1956 (In French) [Paris, France].

The authors describe the initial histological lesions in the so-called enlarged liver of the chronic alcoholic. The study was based on the findings obtained in 22 patients by puncture biopsy, hepatic radiography, and electrophoresis. Two kinds of subacute hepatitis were detected: one is characterized by a general cellular clarification and the other by a steatotic state that is essentially a cytolytic hepatitis with fatty infiltration. Both have in common a characteristic biological aspect: filtration tests (water, galactose, hippuric acid) show disturbance, but flocculation tests are normal. Electrophoresis shows a constant and important diminution of alpha[1] globulins contrasting with various modifications of albumin and of beta and gamma globulins, which makes this condition different from cirrhogenous hepatitis and cirrhosis. In both kinds of subacute hepatitis the bromsulphonphthalein test is always normal and so is the red colloidal test. In three cases of subacute steatotic hepatitis treated by lipotropic medication, the steatosis disappeared from the histological section, but the picture of cytolytic hepatitis persisted and the functional disturbances present at the start of treatment remained unchanged. This supports the belief that subacute steatotic hepatitis is a cytolytic hepatitis with fatty infiltration. The syndromes may regress slowly under appropriate medication and after elimination of the alcoholic toxin, or they may develop into a mixed parenchymatous hepatitis preceding the cirrhotic process. This development can be detected by the MacLagan and red colloidal tests sooner than by the bromsulphonphthalein test.

The place of publication of the periodicals appears in brackets preceding each abstract.

Periodicals on file in the Library of the American Medical Association may be borrowed by members of the Association or its student organization and by individuals in continental United States or Canada who subscribe to its scientific periodicals. Requests for periodicals should be addressed "Library, American Medical Association." Periodical files cover 1947 to date only, and no photoduplication services are available. No charge is made to members, but the fee for others is 15 cents in stamps for each item. Only three periodicals may be borrowed at one time, and they must not be kept longer than five days. Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Angina Decubitus: A Clinical Appreciation. J. S. Watson. Ohio M. J. 52:581-588 (June) 1956 [Columbus, Ohio].

The author presents the histories of four patients with angina decubitus. He stresses the nocturnal (recumbent) nature of the episodes, the prolonged duration, the vasomotor phenomena (flushing), the activity of the patient, and the ineffectiveness of nitroglycerin. He calls attention to the paucity of information regarding angina decubitus in modern text books. He differentiates angina decubitus from angina of effort and from myocardial infarction by listing the characteristic aspects of each of these three conditions. Angina decubitus occurs in the presence of coronary artery disease as well as in the presence of aortic valvular disease (aortic insufficiency). As regards the treatment, the response to a low-sodium diet is gratifying. The etiology may be explained on the basis of salt and water retention accompanying subclinical congestive heart failure with diminished cardiac output and markedly diminished renal function. Pituitary and adrenal cortical participation seems possible. Exchange resins and acetazolamide (Diamox) were not used in the treatment of these patients, but they might be of value in the further elimination of sodium and water from the body. Heparin was used in one patient, but the effect could not be determined. One should not forget the guarded prognosis, at least during the period of transition, and the unquestionable spontaneous improvement that may occur no matter how the patients are treated.

Disseminated Pulmonary Calcification: Its Association with a Positive Reaction to Histoplasmin Antigen. M. H. Joress and B. P. Bushueff. New England J. Med. 254:1053-1058 (June 7) 1956 [Boston].

Antigen skin testing in the presence of disseminated pulmonary calcification shows a high prevalence of histoplasmin sensitivity. Although infection with Histoplasma capsulatum occurs most frequently in the central states, a number of veterans have been studied since the end of World War II in the chest section of the outpatient department of the Veterans Administration hospital, West Roxbury, Mass., in order to determine the significance of certain abnormalities that were noted on the chest roentgenograms during service or at the time of separation. The authors considered the disseminated calcifications in these young, obviously healthy veterans to be the end-result of previously active histoplasmosis. A variety of designations had been used when the abnormal shadows were first noted in the service hospital or discharging station, such as "healed miliary tuberculosis," "sarcoidosis," "pneumonoconiosis," "miliary calcifications," and "arrested tuberculosis." In studies on 20 veterans with disseminated calcification, they ascertained the birthplace and the residence before service; findings on the induction films; exposure to soil dust before service; history of respiratory illness before or during service; whether the veteran had been exposed to a respiratory disease epidemic; whether mycotic infection was considered at the time of interpretation of the roentgenograms during the service; and whether the veteran could currently react to tuberculin, coccidioidin, and histoplasmin. In 15 patients, tests were made to ascertain whether antibodies were still present in the blood serum. The presence of antibodies was demonstrated in two patients 12 and 11 years after the initial episode of respiratory infection. In the first case, considered "doubtful," the titer was 1:4; in the second, considered "positive," the titer was 1:14.

The authors conclude that, although infection with Histoplasma capsulatum occurs most frequently in the central states, the possibility of this infection occurring in other locations should be kept in mind when the clinical history points to exposure to dust contaminated by the excreta of chickens, pigeons, and bats. Residua of the infection may be located in hilar lymph nodes or may be seen as a granulomatous lesion in the lung, but they are most commonly found as disseminated calcification in a portion of a lung or, more frequently, throughout the entire parenchyma. Antigen skin testing is paramount in differentiating infection due to Mycobacterium tuberculosis and H. capsulatum. Although complement-fixing antibodies are seldom demonstrated many years after the initial infection, it is important to examine the serum in suspected cases. Few patients showing residual histoplasmosis have any knowledge of having experienced serious respiratory illness in the past. Some are aware of past exposure to contaminated soil dust. Most of those with healed lesions have no knowledge of past respiratory disease. The clinician and roentgenologist must maintain a high degree of suspicion if the presence of active, and particularly of inactive, phases of infection with H. capsulatum is to be detected. If it is kept in mind, this disease is less likely to be confused with calcific nodulation from other causes.

Bed Rest in the Treatment of Pulmonary Tuberculosis. W. F. Tyrrell. Lancet 1:821-823 (June 2) 1956 [London, England].

In May, 1954, it was possible to admit to sanatoriums only some of the patients with pulmonary tuberculosis in Glasgow; the remainder were treated as outpatients. From a public health viewpoint this situation was unfortunate, but it offered an opportunity of assessing the therapeutic value of bed rest. It was decided to admit to hospital every alternate new patient in the Northern area of the city and to treat the others as ambulant outpatients. The criteria for acceptance into the trial were that the patient (1) had active pulmonary tuberculosis, (2) was aged 14 to 54, (3) was not living in lodgings, and (4) was ambulant when first seen. Those treated as inpatients were admitted to the sanatorium within two weeks of diagnosis and were kept on strict rest in bed. The outpatients were encouraged to remain up and about; and all except five, who were treated similarly by their own doctors, reported to the hospital for injections of streptomycin. Apart from the amount of exercise allowed, the inpatient and outpatient groups had identical investigation and treatment. Altogether, 141 patients completed three months' treatment, and 94 of these completed six months' treatment. In these 94 patients, the chemotherapy consisted of 1 gm. of streptomycin and 400 mg. of isoniazid on the same day twice weekly; the remaining 47 patients, who have so far completed only three months' treatment, received the same chemotherapy on five days each week.

After three months' treatment, progress, assessed by reduction of erythrocyte sedimentation rate, sputum conversion, cavity closure, and over-all radiographic improvement, was as good in 70 ambulant outpatients as in 71 patients on strict bed rest in hospital. After six months' treatment, no difference was found between 45 patients on strict bed rest in hospital and 46 ambulant outpatients as regards reduction of erythrocyte sedimentation rate, sputum conversion, and over-all radiographic improvement; but cavity closure was commoner in the patients on strict bed rest than in the ambulant outpatients. The author suggests that, before bed rest in the treatment of pulmonary tuberculosis is abandoned, it will be necessary to study the long-term results in a larger number of patients; but it seems that, if the results in this preliminary study are confirmed, patients who have ceased to excrete tubercle bacilli might be allowed to resume their everyday occupations much earlier than is now generally thought desirable. In addition, patients with pulmonary tuberculosis might be allowed much greater physical freedom than at present, with resultant lessening of the burden on nursing staff and diminished tedium for the patients. Where domestic conditions are suitable, home treatment could confidently be carried out on an even larger scale than at present.

SURGERY

Abdominal Pain Following Surgical Correction of Coarctation of the Aorta: A Syndrome. D. M. Ring and F. J. Lewis. J. Thoracic Surgery 31:718-724 (June) 1956 [St. Louis].

Seventy-three patients with coarctation of the aorta were operated on at the department of surgery of the University of Minnesota, Minneapolis. Eighteen patients in this group had significant abdominal symptoms and findings in the early postoperative period. The patients were divided into three groups, depending on the intensity of the signs and symptoms. The first group consisted of one female and nine male patients between the ages of 2½ and 34 years who complained of generalized abdominal pain during the first three postoperative days. There was abdominal distention, gastric dilatation, abdominal

tenderness, ileus, or vomiting. Leukocytosis was present and was associated with mild fever. These complications responded to restriction of oral intake, gastric suction, and intravenous administration of fluids. A second group of four male patients between the ages of 4 and 36 years had difficulties that were similar but of a more serious nature. Symptoms appeared in the first postoperative week and persisted for 7 or 10 days. Recovery resulted in all from conservative treatment. The third group consisted of four male patients between the ages of 3 and 46 years who underwent laparotomy within two weeks after surgical correction of the coarctation of the aorta. A tentative diagnosis of appendicitis had been made in three. In two patients, necrotizing panarteritis indistinguishable from periarteritis nodosa was observed with infarction of portions of the small intestine. One of these patients died of a ruptured splenic aneurysm and the other recovered after resection of 38 cm. of the small intestine. In the third patient the laparotomy findings were negative, but he died one month later from a ruptured dissecting aneurysm of the thoracic aorta. Only enlarged mesenteric lymph nodes were observed on laparotomy in the fourth patient, who subsequently recovered.

The one common factor in all the patients was the sudden increase in pulsatile pressures in the arterial system distal to the coarctation. The signs and symptoms were confined to the visceral areas subject to this increased pressure-head, and particularly to the structures supplied by the superior mesenteric artery. The abdominal pain was possibly related to the arterial distention stimulating viscerosensory fibers in the vessel wall. It seems that the patients with significant abdominal findings represented a varying pathological response to the elevated arterial pressure in the postcoarctation vascular system ranging from temporary functional disturbance to local lysis of overstretched medial muscular fibers, vascular occlusion, and tissue death. Cardiovascular surgeons should be on the alert for this complication, which deserves the term "syndrome." There is no explanation for the preponderance of males among these patients.

Bilateral Resection in Pulmonary Tuberculosis. S. Nishi, A. Sato, M. Iwabuchi and others. J. Thoracic Surg. 31:672-685 (June) 1956 [St. Louis].

Fifteen men and seven women between the ages of 18 and 40 years with pulmonary tuberculosis underwent bilateral resection at the National Okayama Sanatorium in Japan and were followed up for 8 to 24 months after the operation. The extent of the lesion, its site, the thickness of the pleural membrane, the movement of the diaphragm, the condition of the bronchi, and the patient's general condition were considered in selecting the patients for bilateral resection. A separate bronchospirometric examination for each lung was carried out before the operation. Bilateral resection was indicated in patients who did not respond to collapse therapy or in those in whom the response was doubtful, in those in whom thoracoplasty had previously been indicated but who also needed some surgical treatment contralaterally, and in patients in whom the localized lesion was stable and had a diameter of more than 2 cm.

Bilateral lobectomy was performed in 5 patients, lobectomy and segmental resection in 7, and bilateral segmental resection in 10. Simultaneous bilateral segmental resection was performed in two patients. The postoperative course was uneventful, without dyspnea or cyanosis. In 13 patients, two operations were done at intervals that varied from three to six months in 7 patients and were less than three months in 6. Operation should be performed first on the side with the larger focus, and, if the degree of the disease is about the same on both sides, the anatomic relationship and the influence of the cardiac function should be considered. The operation was usually performed first on the right side. There were no postoperative deaths or bronchial fistulas. Empyema occurred in one patient after the second operation, but it was temporary and localized. Reactivation of the focus in the contralateral side occurred after the first operation, and because of this the proposed area for resection in the contralateral side had to be enlarged. Postoperative complications did not occur in the other patients. Postoperative smears and culture tests yielded negative results in all patients except one, in whom the culture test gave a positive result. Symptoms subsided in 10 patients, who have resumed their usual way of life, and the remaining 12 patients will be discharged soon to resume normal activities. If the patients are selected for the operation with care, bilateral resection seems to be successful in returning these patients to a normal life.

Surgical Management of Neoplastic Pulmonary Metastases. W. J. Strieder. New England J. Med. 254:1059-1062 (June 7) 1956 [Boston].

Statistical reports suggest that radiographic demonstration of increased density in the pulmonary field, after the apparently successful extirpation of a primary growth elsewhere, may indicate another primary tumor, which may be benign, as in 4 of the 20 patients with whom this report is concerned. In two patients, the tumors, thought to be metastatic from the breast, proved to be bronchial adenoma; one was a hamartoma, and another was a nonresectable primary adenocarcinoma of the lung. Any demonstrable metastatic lesion may be a solitary one, and its extirpation may result in a cure. The author discusses criteria for selection. Age is not an important factor. The evaluation of the pulmonary function by the usual ventilatory studies, as well as bronchospirometry, is important when the possibilities of total pneumonectomy and bilateral resection are entertained, particularly in elderly patients who may have emphysema. Efforts should be made to exclude from operation patients with hopelessly disseminated disease. Laminography of the lungs, bone-marrow biopsy, roentgenographic examination of the skeleton, and acid and alkaline phosphatase determinations should be carried out routinely before operation is decided on. The original lesion as well as the distribution of the pulmonary metastases should be taken into consideration. Minor found that pleural involvement existed in about a third and involvement of the mediastinal lymph nodes in nearly a fourth of 77 patients with cancer of the breast. Consequently a patient with a "solitary" pulmonary metastasis from cancer of the breast with pleural effusion seems an unlikely candidate for resection. Hypernephroma, on the other hand, has a tendency to produce solitary metastases with long-term survival after resection. Resection of both upper lobes for metastatic lesions secondary to neurogenic sarcoma has also been known to produce long-term survival. The author feels that total pneumonectomy might be indicated for a solitary metastasis so situated that only total pneumonectomy will suffice to remove it, provided pulmonary-function studies indicate that the procedure will be tolerated. Resection of metastatic pulmonary lesions may be undertaken to provide palliation without hope of cure in complications such as hemorrhage and suppuration.

Twenty-two resections of pulmonary tissues were carried out in 20 patients with proved metastatic pumonary disease. There were 2 wedge resections, 2 segmental resections, 15 lobectomies, and 3 total pneumonectomies. No conclusions can be drawn about survival time in relation to type of operation. It appears that lesser resections can be done for metastases in view of the fact that the pathways of extension in metastatic disease in the lung are less likely to be along the lymphatics than in primary neoplastic disease of the lung. Although no hard and fast criteria can as yet be established for operations in metastatic pulmonary disease, the results of this series and others appear to justify the continued use of pulmonary resection in selected cases for metastatic neoplastic pulmonary disease.

The Significance of Pulmonary Coin Lesions. P. W. Johnston and J. A. Weinberg. West. J. Surg. 64:318-320 (June) 1956 [Portland, Ore.].

Seven hundred forty cases of pulmonary coin lesions were collected from the literature, to which 44 cases of coin lesions from the Long Beach Veterans Administration hospital in California were added. A practical definition of a pulmonary coin lesion is that it is a round or oval-shaped, solitary lesion, completely within the substance of the lung, with fairly well-defined borders, free of complications such as pleural effusion, atelectasis, or cavitation, and usually but not necessarily free of symptoms. The study of these 784 cases showed that 39.2% of the coin lesions were malignant and 39% were granulomas. Included among the malignant lesions were primary carcinoma of

the lung, bronchial adenoma, primary sarcoma of the lung, and metastatic pulmonary lesions. Because of this high incidence of malignancy and chronic infection in coin lesions, and because the clinical history, physical examination, and even special diagnostic procedures such as intradermal sensitivity tests, laboratory examinations of sputum, bronchoscopy, or roentgen techniques are of no real assistance in making the diagnosis, exploratory thoractomy and diagnostic biopsy are advisable as aids to definite diagnosis and surgical therapy when indicated. Pulmonary resection is very important from a therapeutic point of view for malignancy and for tuberculoma and to a lesser degree for other benign conditions. The principles adopted should be the same as those universally accepted in treating discrete nodules of the breast.

Sarcomas of Soft Tissues: Pitfalls in Their Diagnosis and Management: A Preliminary Report on 353 Cases. C. E. Nelson, H. C. Prout and P. H. Deeb. West J. Surg. **64**:329-335 (June) 1956 [Portland, Ore.].

A preliminary report has been presented on 353 cases of soft tissue sarcoma reported to the California tumor registry by two hospitals in Los Angeles. The tumors were classified according to their tissues of origin as fibrosarcomas, sarcomas of muscle tissue, adipose tissue sarcomas, sarcomas of pheripheral nerves, malignant tumors of blood and lymph vessels, synovial tissue sarcomas, and undifferentiated and mixed cell types of sarcomas. The largest group, composed of 230 cases, was that of malignant lymphomas. The high incidence of benign soft somatic tumors and the rarity of sarcomas is no doubt responsible for frequent errors in the diagnosis and treatment of these growths. Improper first attack on the tumor favors local spread and distant metastasis. Biopsy is indispensable for accurate diagnosis and treatment. Fibrosarcoma, aside from the lymphomas, is the commonest form of sarcoma. Its spread extends far beyond the visible limits of the tumor. This requires the removal of the surrounding muscles, as well as the entire fascial plane. Although hematogenous spread is the usual means of spread, certain tumors, notably rhabdomyosarcoma, sarcomas of blood and lymph vessels, and occasionally liposarcoma and fibrosarcoma, metastasize to lymph nodes.

Irradiation therapy has a useful place in the treatment of some inoperable sarcomas and is usually the treatment of choice in lymphoblastomas, lymphocytic and giant follicular reticulum-cell sarcomas, and mycosis fungoides. Embryonic liposarcomas may be quite radiosensitive. It is imperative to have frequent periodic follow-up examinations, including x-rays of the chest, so that if metastatic lesions are found in the lungs, lobectomy or pneumonectomy, which is of great palliative or even curative value, may be performed. Two cases of fibrosarcoma in women aged 21 and 54 years, respectively, which illustrate the common pitfalls in diagnosis and treatment, are described. In both patients clinical diagnosis was wrong and in neither was sarcoma suspected. In the first patient, the initial treatment was inadequate because of an error in pathological diagnosis, but even after the proper diagnosis had been made, the surgical attack was still inadequate. In the second patient, the error lay in failure to make a rapid frozen section at the time of the first operation, thus delaying definitive treatment. Nine months elapsed from the time the recurrent lesion in this patient was removed until another roentgenogram of the chest was taken; and, although the lung metastasis was unilateral, it had involved the parietal pleura by the time the second operation was performed.

Acute Hemorrhagic Pancreatitis Following Biliary-Tract Surgical Procedures. W. G. Diffenbaugh and E. L. Strohl. A. M. A. Arch. Surg. **72**:931-941 (June) 1956 [Chicago].

Acute hemorrhagic pancreatitis is occasionally a tragic complication of upper abdominal surgery. Such a catastrophe is probably due to vascular damage to the pancreas associated with some form of trauma to the duct of Wirsung or to the duct of Santorini. The types of trauma to the pancreatic duct that may produce obstruction include (1) edema or hemorrhage following instrumental exploration of the distal common duct, (2) ligation or angulation of the ducts of Wirsung or Santorini, and (3) pressure of a long-arm T-tube or catheter that passes through the papilla into the duodenum. A number of cases of acute hemorrhagic pancreatitis have been reported after the use of such tubes, and the authors present the histories of four additional patients, all of whom died; the diagnosis of acute hemorrhagic pancreatitis was confirmed at autopsy in all four patients.

In a fifth patient, the sphincter of Oddi was divided. Absorbable surgical (catgut) sutures were used to approximate the duodenal mucosa and the mucosa of the edges of the cut sphincter. Twenty-four hours postoperatively there was severe pain. At the end of 72 hours, it was apparent from the increased pulse rate, fall in blood pressure, and distention that some abdominal catastrophe had occurred. Abdominal exploration revealed acute hemorrhagic pancreatitis with fat necrosis. The gallbladder was greatly distended. Cholecystostomy and drainage of the abdomen was carried out. There was much drainage of flecks of necrotic pancreas, which persisted for four months. Recovery occurred. Sutures should not be used after sphincterotomy. The suture may retain the edema and obstruct the pancreatic duct.

Sphincter-Preserving Operations for Cancer of the Rectum: Special Reference to the Incidence and Survival Rates. R. R. Best and J. A. Rasmussen. A. M. A. Arch. Surg. **72**:948-956 (June) 1956 [Chicago].

Sphincter-preserving operations are becoming more widely accepted for patients with carcinoma of the rectum and rectosigmoid area. A lesion below the peritoneal floor and yet more than 5 cm. above the external sphincter margin demands a different surgical approach from that required for a lesion that is more than 10 cm. above the sphincter margin and at or above the peritoneal floor level. For this latter lesion, the rectosigmoidectomy no. 1 procedure, which is an abdominal dissection, resection, and anastomosis, is the operation of choice. When the lesion is below the peritoneal floor and more than 5 cm. from the external sphincter margin, the rectosigmoidectomy no. 2 procedure, an abdominal dissection with posterior resection and anastomosis, is the operation of choice.

Observations are presented on 189 patients who were seen between October, 1945, and Jan. 1, 1953, and who had a diagnosis of cancer of the lower sigmoid, rectosigmoid, or rectum. Of this number, 130 were private patients and 59 were observed at the university clinic. These two groups are reviewed separately. One of the 59 clinic patients refused treatment. Fifty-four of the 58 were operated on, but 10 had an exploratory operation only, a colostomy, or a cecostomy. Forty-four patients, or 81.4%, had resectable lesions, but some of the resections were palliative only, because of evidence of distant metastasis. A sphincter-preserving operation was performed on 26 patients and an abdominoperineal resection with sacrifice of the sphincter mechanism in 18. There was one death in the abdominoperineal group and two deaths in the rectosigmoidectomies with sphincter preservation group. A rectosigmoidectomy no. 1 procedure was accomplished in 20 patients. Not many rectosigmoidectomy no. 2 procedures were carried out on the patients at the university clinic. Two of the clinic patients underwent rectosigmoidectomy no. 3, a poor operation for cancer. One hundred twenty-one of the 130 private patients were operated on. There were 111 resectable lesions, a 91.7% resectability rate. A sphincter-preserving operation was accomplished in 84 patients, and an abdominoperineal operation was performed in 27 patients. In the 84 patients with sphincter-preserving operations, the rectosigmoidectomy no. 1 was performed in 63 instances. In nine patients of this group the lesion was so extensive or liver metastasis so evident that the resection and anastomosis was merely a palliative procedure. The rectosigmoidectomy no. 2 procedure was carried out as a curative operation in 19 patients. The rectosigmoidectomy no. 3 operation was used in two of the private patients.

The survival rates for two, three, four, and five years in patients with rectosigmoidectomy operations with preservation of the sphincter mechanism are comparable to those for patients with abdominoperineal resections. At the five-year period, this approximates 54%. The mortality rate tends to be just a little higher for the resection and anastomosis procedures, although, if earlier deaths, when technical factors were not so clearly understood, are excluded, the mortality rate is practically the same. Suture-line complications are commoner, but by posterior drainage and proper decompressive measures they are usually only of a temporary nature. Sexual potency appears to be retained in about 75% of the patients following rectosigmoidec-

tomy with sphincter preservation, as compared with a loss of sexual potency in about 75% or more of patients with abdominoperineal resection. While both surgeon and patient are gratified when a colostomy can be avoided, the surgeon must not make any absolute promise to the patient before surgery about avoiding a temporary or permanent colostomy, for this would compromise his good judgment as to the choice of procedure at the operating table.

Blood-Culture Studies of the Portal Vein. F. W. Taylor. A. M. A. Arch. Surg. **72**:889-892 (June) 1956 [Chicago].

According to Taylor, it is generally believed that the liver rids the portal blood of many bacteria. There is little doubt that the liver is capable of this sterilizing action in persons with acute infections or ulcerative lesions of the intestine, but there is considerable doubt whether this action takes place in the healthy person and whether bacteria are normally poured into the liver by way of the portal vein. Some years ago, the author attempted to prove or disprove the thesis that the portal vein normally carries bacteria. The cultures of portal blood taken at that time were sterile. The means of obtaining these cultures were laborious. Two factors induced the author to resume these studies: (1) the practicability of placing a plastic tube in the portal vein from which random samples of blood could be removed for interval culture; (2) a recent report that was contrary to the author's earlier findings.

A total of 167 portal-vein cultures were taken from 21 patients. Of these, 101 were aerobic and 66 were anaerobic. In all but two of the patients the blood samples were obtained by means of the indwelling-plastic-tube method. In these two, portal blood was obtained at operation before proceeding with a routine cholecystectomy. All 167 samples were sterile. It is believed that 9 and possibly all of the 10 positive cultures were due to contaminations. The author concludes that blood carried in the portal vein is normally sterile. The method of obtaining repeated blood samples opens avenues for further bacterial study of portal blood in persons with various intestinal infections.

Pseudomembranous Enterocolitis: Its Etiology and the Mechanism of the Disease Process. J. Van Prohaska, E. T. Long and T. S. Nelsen. A. M. A. Arch. Surg. **72**:977-983 (June) 1956 [Chicago].

Increasing clinical evidence has been gathered during the past few years seriously implicating Micrococcus pyogenes (Staphylococcus aureus) as the etiological agent responsible for the often fatal surgical complication known as pseudomembranous enterocolitis. This disease entity has been most frequently described as a necrotizing colitis or enteritis following major abdominal surgery in patients who were prepared for operation by the oral administration of antibiotics. The authors believe that it is incorrect to associate this serious complication exclusively with abdominal operations or with the intestinal use of antibiotics. The variety of conditions under which pseudomembranous enterocolitis appears prevents easy solution of the problem of its etiology. Confusions stem from the observations that the disease sometimes follows surgical operations and sometimes does not; at one time it is related to antibiotic therapy and at other times not. The disease cannot be considered a definite entity until these opposing facts are made to fit into a pattern that can encompass all variations. The authors present clinical and experimental evidence in support of the following contentions: 1. Pseudomembranous enterocolitis is an infectious disease produced by M. pyogenes. 2. M. pyogenes does not establish itself in an intestinal tract containing the usual bacterial flora. 3. The shock and the fatal course of the disease are enhanced by the micrococcic enterotoxin. 4. The effect of the enterotoxin may be counteracted by giving corticotropin (ACTH), a life-saving therapy.

Some investigators have designated erythromycin as an antibiotic that has a specific action against micrococci and therefore advised it as the only drug in the treatment of pseudomembranous enteritis. This may be true, but in most instances the enteritis pursues a rapid downhill course, so that there is no time to wait until erythromycin attains sufficient concentration to destroy the organism. Even if this could be accomplished, the host would still have to get rid of a quantity of residual enterotoxin. If corticotropin is given, the "neutralization" of the toxins appears to be immediate. The erythromycin, of course, should also be given for its lethal action on the micrococci, if they are sensitive to it. Benign, lingering diarrheas appearing after antibiotic therapy are not to be confused with pseudomembranous enteritis or colitis. These benign diarrheas are produced by a simple bacterial derangement of the colonic flora without the development of enterotoxin-producing micrococci.

NEUROLOGY & PSYCHIATRY

Poliomyelitis in Missouri in 1955: An Epidemiologic Summary. E. A. Belden. Missouri Med. **53**:456-458 (June) 1956 [St. Louis].

When the question of safety of poliomyelitis serum arose in April, 1955, as a result of the occurrence of poliomyelitis in recently inoculated children in certain Western states, a nationwide investigation of all cases of poliomyelitis was instituted. As a result of the investigation in Missouri, the epidemiological data on poliomyelitis in Missouri in 1955 are more detailed and accurate than for any previous year. Poliomyelitis occurred in 11 children, who had been vaccinated against poliomyelitis. The possibility of infection by the vaccine must be considered in three children, in whom the poliomyelitis began within 28 days of vaccination. One of these three children had the paralytic, the other two the nonparalytic, form of poliomyelitis. The available evidence indicated that in the patient with the paralytic form the poliomyelitis may have resulted from the vaccination, but in the two with the nonparalytic form this does not seem probable. The eight cases of poliomyelitis in vaccinated children occurring more than 28 days after last vaccination are classified as vaccine "failures," although all of them had received only one injection of vaccine prior to the diagnosis of poliomyelitis.

In children between the ages of 6 and 10 years, the over-all poliomyelitis attack rate was four times as great and the attack rate of paralytic poliomyelitis was six times as great in the unvaccinated as in the vaccinated. This represents a reduction of 84% in paralytic poliomyelitis in the vaccinated group. Poliomyelitis virus was recovered from 38% of the patients with the paralytic form tested for it and from 19% of those with the nonparalytic form tested for it. The rather low percentage of isolations in patients with the nonparalytic form points up the relative difficulty of making a firm clinical diagnosis in the absence of paralysis. However, the recovery of virus in a significant number of nonparalytic and asymptomatic cases is confirmatory evidence of infection without paralysis. The determination of serum neutralization (antibody) titers of paired serums was of little value in confirming clinical diagnoses. This was largely because of the difficulties involved in obtaining the first specimen early in the disease and the second specimen two to four weeks later, when most patients had left the hospital. The author believes that the examination of repeated specimens of feces for virus isolation and typing would be a more effective and practical aid in the diagnosis of poliomyelitis than neutralization tests on paired serums.

The Recovery of Poliomyelitis Viruses from Fecal Samples of Poliomyelitis Patients and Household Contacts. C. A. Miller and P. Kamitsuka. Am. J. M. Sc. **231**:607-615 (June) 1956 [Philadelphia].

During the 1954 field trial of the poliomyelitis vaccine, the virus research laboratory of the University of Kansas participated in the evaluation of the vaccine, testing more than 243 stool specimens from patients and household contacts for the presence of poliomyelitis virus. The vaccine evaluation center had requested that studies be done on first, second, and third grade children who resided in the study areas and in whom clinical evidence of poliomyelitis developed. Ninety-seven children were studied on this basis. This report summarizes data on the recovery of poliomyelitis virus from fecal specimens and correlates these findings with the epidemiological findings. Family infections due to poliomyelitis were clinically apparent in about one-third of the families studied. Symptoms in the different members of a family tended to appear concurrently. Clinically apparent poliomyelitis developed most frequently (in 50%) in children 4 and 5 years old who were in contact with a patient who was known to have poliomyelitis. The stool specimens of 79% of patients with the paralytic form of poliomyelitis yielded poliomyelitis virus, whereas this was the case

in only 50% of the patients with the nonparalytic form, indicating perhaps that a number of these infections were caused by some agent other than poliomyelitis viruses. One-third of all persons having household contact with a patient in whom poliomyelitis was clinically diagnosed were shown to have poliomyelitis virus in their stool specimens. The virus carrier rate was much greater than this among (a) household contacts who had some symptom indicative of illness, (b) those who where exposed to a paralytic patient, and (c) those under 10 years of age. Excretion of virus in fecal samples was at a high level for the first three weeks of convalescence, after which the recovery rate dropped sharply. The percentage of asymptomatic household contacts excreting virus showed a decided peak three weeks after the first onset of symptoms in the household. Among the household contacts, 80% of the virus carriers were free of symptoms of illness. The administration of gamma globulin to household contacts appeared not to interfere with the demonstration of virus in their fecal specimens.

GYNECOLOGY & OBSTETRICS

Prolapse of Fallopian Tube After Vaginal Hysterectomy: Report of Three Cases. W. O. Johnson. J. Kentucky M. A. 54:503-505 (June) 1956 [Louisville, Ky.].

The author reports on three women in whom prolapse of the fallopian tube occurred after a vaginal hysterectomy. The condition is not so rare as reports would indicate. He lists the following as causal factors of prolapse of the uterine tube: damage to the rectouterine pouch (cul-de-sac); poor condition of the tissues; postoperative infection; postoperative ectopic pregnancy; an interposition operation; inadequate closure with and without drainage; and hematoma. The symptoms of prolapse of the uterine tube appear from one to four months after the operation, and consist generally of a persistent, profuse vaginal discharge and pain and tenderness in the dome of the vagina after long standing or on touching the dome of the vagina.

The author considers the following method as the best treatment for the condition. The patient is anesthetized. After the vagina is cleansed, the prolapsed tube is pulled out as far as possible, cut off with a cautery or knife, ligated, and then allowed to retract into the dome of the vaginal vault. It will then granulate, and the discharge will stop. Some prolapsed tubes can be removed in the office by treating them repeatedly with cautery or by silver nitrate sticks until they granulate in and are covered with vaginal mucous membrane.

The Hydrazinophthalazin Compounds in the Treatment of Hypertension in Obstetrics and Gynecology. F. Zuinzani. Minerva ginec. 8:230-233 (March 15) 1956 (In Italian) [Turin, Italy].

Sixteen patients with pure hypertension or obstetric hypertension and 14 with essential or renal hypertension were treated with hydrazinophthalazin compounds. The drugs were particularly effective in obstetric hypertension, essential hypertension of pregnancy, essential hypertension in general, and climacteric hypertension. They had no effect on nephrogenic hypertension. The values decrease after doses of 25 to 50 mg., which can be given at once or in small doses until a maximal dose of 200 mg. per day is reached. High doses do not have a greater hypotensive effect, but they make the effects of the drug last longer. The effect lasts from 1 to 10 hours when the drug is given orally. The maximal hypotensive value after a single dose was 50 mm. Hg for the systolic pressure. The mean pressure after the treatment was 30 mm. Hg. A value of 35 and a mean of 15 mm. Hg was observed in the diastolic pressure. Doses, length of effect, and hypotensive effect are not directly related; each is related to factors peculiar to each patient. Side-effects such as headache, nausea, and tachycardia are also related to the sensitivity of the patient. Apresoline has more definite side-effects (always present in patients with essential hypertension). Side-effects were marked in patients with heart disease and in patients with nephrogenous or arteriosclerotic hypertension. Eclampsia did not occur even when pressure values were above 160 mm. Hg. The pulse rate increased in almost all patients. Treatment must be prolonged up to a year to stabilize the hypotensive effect of the drugs. The drugs can be used electively in the prophylactic treatment of gestoses.

PEDIATRICS

Management of Hypothyroidism in Infancy and Childhood. R. E. Cooke and E. B. Man. Pediatrics 17:617-631 (May) 1956 [Springfield, Ill.].

Studies were undertaken to evaluate the adequacy of therapy in infants and children with congenital hypothyroidism, with respect to both promptness in beginning the therapy and the adequacy of dosage. Symptoms of hypofunction of the thyroid appeared during the first year of life, and it is assumed that all of these infants and children were born with some defect in function of the thyroid and had congenital hypothyroidism. The 24 children studied ranged in age from 2 days to 11 years. Hypothyroidism was suspected in these patients because of one or more of the following signs: enlargement of the thyroid, large tongue, furrowed brow, thick skin, puffy eyes, carotenemia, constipation, poor feeding, disturbance in growth, or psychomotor retardation. In most cases roentgenographic examination of the bones and detailed psychometric examinations were carried out. The children were treated with desiccated thyroid. Determinations of the serum butanol-extractable iodine (BEI) levels were used as a basis for diagnosis and in most instances for regulation of replacement therapy. In all patients for whom the serum butanol-extractable iodine level was determined before therapy, the values were significantly below the normal range for children and varied between 0 and 2.9 mcg. per 100 ml. After treatment with 90 to 240 mg. of desiccated thyroid per day, the older children had serum butanol-extractable iodine values within or slightly above the normal range of 4.5 to 7.3 mcg. per 100 ml. The five hypothyroid infants, who were less than one year old, tolerated and required rapidly increasing amounts of desiccated thyroid that varied between 45 and 90 mg. daily. Early therapy with large quantities of desiccated thyroid is suggested to obtain optimal mental development. It is obvious from these studies that the use of a laboratory procedure such as the determination of the serum butanol-extractable iodine level is essential in the early diagnosis and in the regulation of treatment of hypothyroidism in infancy and childhood.

Sudden and Unexpected Death in Infancy and Childhood. L. Adelson and E. R. Kinney. Pediatrics 17:663-699 (May) 1956 [Springfield, Ill.]

In 1951, under the sponsorship of the U. S. Public Health Service, a program was organized in which the medicolegal agencies of Cuyahoga County, Ohio, of the Borough of Queens of New York City, and of Baltimore and Boston were designated to study sudden and unexpected deaths that occur without obvious cause in the first two years of life. This report is concerned with the studies made in Cuyahoga County (population approximately 1,600,000). One hundred twenty-six consecutive cases of sudden and unexpected death in children between the ages of 10 days and 2 years were studied. Anatomic and microbiological studies were carried out, and an investigation was made at the home of each child. Both sexes proved equally vulnerable. Eighty-five per cent of the children were less than 6 months old. The peak incidence of unexpected death was at 2 months. Ninety-nine children were found dead and 27 were observed to die. The same variety and severity of anatomic lesions were found in both categories. Sixteen children in the same age range who died rapidly after known lethal violence were studied as a control group. Of those in the nontraumatic sudden death ("unexplained") series, 106 (84%) revealed microscopic inflammatory changes in one or more sites of the respiratory tract, and histological evidence of inflammatory disease in other organs was seen in many cases. Acute hemorrhagic pulmonary edema was a common anatomic finding (82%). It was usually accompanied by visceral and cerebral congestion and hemorrhages. Staining of the liver for glycogen, determination of the glucose level of the cerebrospinal fluid, and study of the adrenals for sudanophilia and birefringence indicated that these factors are without significance in sudden death in early life. A variety of congenital and acquired abnormalities, the presence of which had been unsuspected, was demonstrated at autopsy. Eleven per cent of the 126 children showed no anatomic abnormalities other than the circulatory phenomena. No single bacterial organism or group of organisms was isolated with consistency from any site. Attempts to isolate viruses were negative.

Antemortem symptoms, circumstances of death, history of contact with infectious disease, and history of repeated respiratory infection were without significance as to the cause of death. Eighty children had histories of mild illness for 48 hours or less prior to death. Fifty-three children had received some form of treatment during this interval. Sixty-nine children had histories of contact with infectious diseases. Forty-one children had past histories of repeated respiratory infections. The children came from every social level; 65% had received good care, while 35% had received poor care. Many of the controls showed inflammatory disease in the respiratory tract similar to that seen in the natural death group as well as anatomic evidence of lethal trauma. The inflammatory lesions are thus not incompatible with life. Several hypotheses are offered in an effort to link microscopic inflammatory respiratory tract changes with hemorrhagic pulmonary edema and sudden death. Anatomic and anamnestic evidence excluded mechanical suffocation by bedding. The investigation revealed no evidence that disease of the thymus, lymph nodes or spleen caused or contributed to the sudden and unexpected death. Although 63% of the children had histories of mild symptoms prior to death, there was nothing to warn of impending death. The authors conclude that, when an infant has died suddenly and unexpectedly, no statement as to the cause of death should be made without complete gross and microscopic studies and a thorough investigation of the scene and circumstances of death.

A New Diagnostic Method in Allergic Disease. A. P. Black. Pediatrics **17**:716-724 (May) 1956 [Springfield, Ill.].

These investigations were undertaken to observe microscopically the effect of allergens upon living warm blood cells of allergic children. In the test described, dried protein, allergen, and plasma from a sensitized or allergic patient are mixed with living leukocytes and platelets either from the patient or a nonallergic donor. The prepared slides are kept at 37 C and observed under the microscope. If specific antibodies to the allergen are present in the plasma, the polymorphonuclear leukocytes and platelets show toxic effects and the cells die within from 15 minutes to several hours, whereas controls remain viable and actively motile. This cytotoxic reaction has been observed with food, pollen, epidermal, and inhalant allergens, and shows such correlation with clinical sensitivity as to be a helpful guide in determining which allergens are likely offenders and which are innocuous in a particular case. A positive reaction does not necessarily mean clinical sensitivity, but, if the reaction is prompt and strong, such sensitivity is likely. If the reaction is negative, clinical sensitivity has not been found except after anaphylaxis. It is believed that the technique described and the observations reported constitute a new and useful diagnostic method in allergic disease.

Some Observations on Headache and Eye Pain in a Group of Schoolchildren. E. L. Hughes and C. E. Cooper. Brit. M. J. **1**: 1138-1141 (May 19) 1956 [London, England].

In 85 of 189 schoolchildren with headache and eye pain, the pain was related to tender areas in the posterior neck muscles, and particularly to the tip of the first cervical transverse process. This type of pain was observed in some children who were only 5 years old. It was often thought by the parents to be connected with the eyes and led to the unnecessary wearing of glasses in some patients. Occasionally it persisted for years and gave rise to the excessive taking of aspirin. In a few children it cleared up spontaneously, while in most it responded to exercises relaxing the head and neck. In order to steady the shoulder girdle, the child was told to stand leaning forward a little with his hands resting on a chair or table low enough to enable the arms to be vertical and rigid, and to flop the head backwards and forwards and then round and round. In some cases the mother was instructed to rub the area over the "trigger-point" to help the relaxation. These exercises were to be done every night, and also if headache threatened. In most patients, the tender areas in the neck muscles together with the tenderness of the tip of the first cervical transverse process disappeared after this simple treatment. The basiocciptial region seems to have received hitherto little investigation. Palpation of this region, the adjoining neck muscles, and the cervical spine does not usually form part of a routine examination. The authors believe that this region deserves systematic examination so that one may know more of its contribution to and connection with the origin of headache in childhood.

Congential Leukemia. S. Fischer. Ugesk. læger **118**:445-447 (May 3) 1956 (In Danish) [Copenhagen, Denmark].

Up to 1952, only 14 cases of congenital leukemia had been reported. Inclusion of the cases that developed during the first days after birth doubles the number. The course of the disease and the results of autopsy reveal the true nature of the disorder. The leukemia is as a rule myelogenic. The manifestations are universal, but most intense in liver and spleen. Localization to the skin is frequent. As a result of thrombocytopenia and damage to the liver, there is often a tendency to bleeding. The infant is as a rule born at full term. Nothing is known concerning familial disposition. The case described was in a well-built, full-term infant. Delivery was normal. Death occurred eight hours after birth. About 40 evenly apportioned bluish-red or brownish-red subcutaneous tumors were covered by intact epidermis. Microscopic examination showed leukemic infiltration everywhere. The tissue anoxia was due to the conglomeration of leukemia cells in the arterioles and capillaries and the related increase in peripheral resistance. The mother's blood picture was practically normal.

DERMATOLOGY

Tinea Pedis in General Practice. W. Gould and M. Schwartz. Practitioner **176**:670-673 (June) 1956 [London, England].

The major problem of tinea pedis is that of relapses, particularly after a period of hot weather. The authors selected a naphthylmethane disulphonate (penotrane), which is available as an aqueous solution (0.1%), a jelly (0.1%), a tincture (0.1%) containing 50% alcohol, or a dusting powder (0.4%). The patients were instructed to observe strict foot hygiene, involving twice-daily foot washing with separate towels, avoiding contact between bathroom floor and mats and the bare feet, and daily changing and washing of socks. The powder was used throughout treatment by dusting on to the feet and into the socks and shoes. Twice daily, morning and night, either the solution, jelly, or tincture was used. The jelly was applied with gentle massage; the solution and tincture were applied with swabs of cotton-wool and allowed to dry before dusting the feet with powder. In most cases the solution was used initially with the powder, as evaporation of the lotion assisted in drying and hardening any sodden white skin. If continued application of the solution tended to produce excessive drying, the emollient jelly was used instead to prevent the skin from becoming brittle and scaly, but the solution was again applied at the first sign of any renewed sogginess.

Of 45 patients treated with penotrane, 36 obtained excellent or good results, 7 fair results, and 2 no result. There were no relapses throughout the summer in any of the patients who had successfully completed treatment by or before May, 1955.

Herpes Gestationis Treated with Hormones. F. Gianotti. Gior. ital. dermat. e sif. **47**:61-68 (Jan.-Feb.) 1956 (In Italian) [Milan, Italy].

The author reports on the treatment of four cases of herpes gestationis. Good results were achieved by correcting the various hormones of the hypophysis-ovary-placenta system, which previously showed deviations from normal. The dermatosis always occurs after the fifth month of pregnancy, except that it may occur earlier in subjects who have already had it during previous pregnancies. Recurrence of the disease after delivery is common. Cutaneous or subcutaneous edema and leukocytosis are always present. Erythrosedimentation increases because of the marked imbalance in the various components of the blood. The author excludes isoimmunization with the Rh factor as an etiopathogenetic factor; only one patient had a negative Rh, but her husband and son were also Rh negative. The dermatosis always occurs in women with marked endocrinologic deficiency. Oligomenorrhea is the first evidence. There is an abnormal growth of hair. Spontaneous abortions or premature abortions for no apparent cause are frequent. Hyperthyroidism is present at times. The value of estrogens excreted in the urine during

pregnancy is high but returns to normal after pregnancy. The excretion of gonadotropin is high; in one patient in the seventh month of pregnancy the value reached 140,000 rat units. All patients treated by the author gave birth to live infants. The dermatosis disappeared in from 10 to 15 days.

PATHOLOGY

L. E. and L. E.-like Cells: A Morphological Study. E. N. Gouldin and L. W. Diggs. South. M. J. 49:560-566 (June) 1956 [Birmingham, Ala.]

Smears of the buffy coat of defibrinated blood of patients with systemic lupus erythematosus were made at 15-minute intervals after collection. The first change observed was a pyknosis of the nucleus. This was followed by a swelling of the nucleus, a disappearance of interlobar filaments, and a loss of distinct chromatin markings. The nuclear alteration in most of the cells was symmetrical, producing lobes having a smooth or homogeneous appearance. In other cells the nuclear alterations were asymmetrical, often involving one portion of the nucleus more than others and producing a flaky or lumpy nuclear appearance. The cytoplasm disintegrated in association with the more advanced nuclear changes. The mass of altered nuclear material was phagocytized, usually by other neutrophils. The phagocytosis of the smooth and homogeneous nuclear masses produced the classical L.E. inclusions as described by Hargraves and associates, whereas the phagocytosis of the flocculent or lumpy masses led to the production of L.E.-like inclusions, which cannot be distinguished from those seen in many nonsystemic lupus erythematosus conditions. The L.E.-like cells differ from the typical L.E. cells in that the inclusions are not smooth and homogeneous but are unevenly stained and have residual chromatin structures. L.E.-like cells frequently have prominent and dark margins, whereas typical L.E. cells have little or no peripheral condensation of chromatin.

With the morphological features of both the L.E. and L.E.-like cells in mind, the cases of 13 patients with systemic lupus erythematosus, 8 of which were confirmed by autopsy, were studied. The number of L.E. cells, L.E.-like cells and rosettes in relation to the neutrophils in L.E. preparations obtained from these patients varied from 0.6 to 13.4 L.E. cells per 100 neutrophils. There was poor correlation between the number of typical L.E. cells, L.E.-like cells, and the number of rosettes. In smears of buffy coat of blood from eight patients with conditions other than systemic lupus erythematosus who had demonstrable L.E.-like cells, rosettes were demonstrable in four. Cells indistinguishable from the typical L.E. cells were observed in one patient with rheumatoid arthritis. The so-called L.E. cells are not specific for systemic lupus erythematosus. The reliability of the diagnosis is increased in proportion to the number of typical L.E. cells seen. The diagnosis should be made with the aid of combined laboratory and clinical findings and not with the aid of morphological studies alone. The reports of the L.E. preparations should state the number of L.E. and L.E.-like cells per 100 neutrophilic leukocytes, based on the examination of 300 or more leukocytes.

On Diagnosing Cancer Histologically. W. W. Park. Lancet 1: 701-704 (May 19) 1956 [London, England].

The pathologist giving a histological diagnosis of cancer is too often regarded as a dispenser of absolute truth. The wide use of, and faith in, the term "histologically proved" is evidence of this attitude. A definite diagnosis of cancer can be made when the alterations in tissue pattern are obvious, and the correlation between these morphological alterations and subsequent death is very high. When a diagnosis of cancer is made at a low level of clinical correlation it is extremely difficult to know how close to the truth we are for the obvious reason that it is almost impossible to distinguish between early diagnosis and wrong diagnosis. If a lesion, erroneously diagnosed as cancer, is completely removed, the records will wrongly show that a cancer has been "cured." If, on the other hand, the histologist has a high diagnostic threshold for cancer, a truly malignant lesion may be diagnosed as "not cancer." The pathologist's difficulty is that he must try to visualize the earliest stages of those abnormal tissue patterns that, when at their maximum in the "obvious" case, form unmistakable evidence of atypical and excessive growth of cells. These patterns are manifest as (1) cell polymorphism accompanied by a varying degree of mitotic activity, and (2) the property that we call "invasiveness." Neither of these properties can be depended upon absolutely.

It may be objected that a proper and comprehensive opinion on a section cannot be given without full clinical data. This is true; but the time for the histopathologist to read the clinical data is after he has assessed the section, not before. Foreknowledge of the clinical data introduces into the mind such a bias that some degree of prejudgment of the section is almost impossible to avoid. The self-discipline involved in "blind" examining has the humbling effect of making the histologist realize how helpless he can be without information about site, age, and other clinical details. The pathologist should persuade the clinician to provide as much clinical data as possible, since, usually, the more help the pathologist receives, the more he can give. However, the pathologist should always examine the sections before he reads the clinical data. The term "histologically proved," when applied to cancer, is admissible only if "proved" is used in its original and now almost obsolete sense of "tried, tested, or assessed." Its equation with "proof" in the legal sense, with the implication that certain objectively defined, specific criteria have been satisfied, is not justifiable.

Mixed Staphylococcal Infections: The Development of Penicillin-Resistant Strains. R. W. Fairbrother. Lancet 1:716-718 (May 19) 1956 [London, England].

While the origin of penicillin-resistant strains of Micrococcus (Staphylococcus) pyogenes var. aureus has not been satisfactorily explained, it has been firmly established that (1) the resistance of naturally occurring strains of this variety of micrococcus to penicillin is due to the production of the enzyme penicillinase, and (2) this enzyme is not produced by strains rendered resistant to penicillin in the laboratory. Thus there are two mechanisms whereby resistance to penicillin is developed. The author deals here with only the naturally occurring penicillin-resistant strains, i. e., the producers of penicillinase. It has been found that these strains are unstable. The present investigation is a continuation of the study of the development of variant strains. Penicillin-sensitive strains of M. pyogenes var. aureus proved to be coagulase-positive, were inhibited by 1/16 to 1/32 unit per milliliter of penicillin, gave a clear zone round the penicillin disks, and did not produce penicillinase. Penicillin-resistant strains were coagulase-positive, produced penicillinase, did not give a clear zone round the penicillin disks, and were not inhibited by at least 10 units per milliliter of penicillin.

Of 550 strains of M. pyogenes var. aureus recently isolated from infections, 312 (57%) were penicillin-resistant. Previous figures for the same hospital were 42% in 1950 to 1951 and 57% in 1953 to 1954. The incidence of penicillin-resistant strains among outpatients was 37%. Penicillin-sensitive and penicillin-resistant strains with the same phage pattern were isolated from the same lesion on 11 different occasions; this suggests a common origin for these organisms. Penicillin-sensitive variants were readily obtained from penicillinase-producing strains by growth at 44 C. Attempts to obtain penicillinase-producing strains from naturally occurring penicillin-sensitive strains were unsuccessful. Such variants were, however, produced by two of eight apparently penicillin-sensitive strains obtained by growing penicillinase-producing organisms at 44 C. It is suggested that M. aureus formerly led a wild existence in which it produced penicillinase, and that this function was later largely, but not entirely, lost by prolonged adaptation to the human nares.

RADIOLOGY

Malignant Tumors of the Mouth. R. Varela Chilese, B. Dosoretz and A. Torres Rojo de Feliu. Rev. Asoc. med. argent. 70:39-50 (March 15-30) 1956 (In Spanish) [Buenos Aires, Argentina].

One thousand, five hundred thirty-five patients with malignant tumors were observed in the oncology ward of the Hospital Rivadavia of Buenos Aires in the period from 1948 to 1955. The tumor was located either in the head or in the neck in 325 patients and, of these, in the nasopharynx in 16 cases. Most

of the patients were between the ages of 31 and 50 years. The patients stated that they had had nose and ear symptoms for more than two years. The tumor was located in the right, left, or middle posterior region of the nasopharynx in seven cases, on the right or left lateral wall in four cases, and on the right, left, and posterior walls of the structure in five cases. A biopsy was made in 10 cases. It revealed a reticulosarcoma in two patients, a lymphoepithelioma and an undifferentiated carcinoma in eight, and a pavement cell carcinoma in two. The treatment consisted of roentgen radiations alone or with radium. The results of the treatment were poor, and none of the patients survived for more than five years. Eleven patients died between a few months and two years after treatment. The five patients who are living with or without symptoms of cancer either are under treatment or have had too short a period of observation for conclusions to be reached. The poor results in this group seem to be due to late diagnosis and insufficient doses and/or poor technique of radium and roentgen therapy. To obtain better results, the following schedule of treatment is planned: The tumors are divided according to type into two groups. Tumors of the first group (reticulosarcoma, lymphosarcoma, lymphoepithelioma, and undifferentiated epithelial tumors) are highly malignant, give early metastases, and are of high radiosensitivity. Regional roentgen therapy, alone or combined with local application of radium, is used in the treatment of this type. Regional roentgen treatment is given in a block from the base of the cranium to the base of the neck. The dose is 3,000 to 3,500 r in three weeks on fields varying between 10 by 15, 10 by 20, or 15 by 20. A very important technical problem is the protection of the eyes, which are included in the treated zone.

Tumors of the second group (differentiated and semidifferentiated pavement cell carcinoma) have moderate radiosensitivity. The daily dose of roentgen rays is 200 or 300 r in each field, which is radiated on successive days until a total dose of 3,000 to 3,500 r per field has been given. By the directed-beam method, the dose for the whole tumor (tumor-dose) is 5,500 r in three weeks or 6,000 r in five weeks. Circular fields of 5-to-6-cm. diameter are the most convenient. The intracavitary radium method consists of placing a lineal source of radium in the nasopharynx. Radium in the nasopharynx can be used as the only treatment in early spinocellular carcinoma or in combination with regional roentgentherapy in undifferentiated or semiundifferentiated carcinoma. The dose of radium intracavitarily placed is 6,000 r in a week by the British method and 8,000 r in a week by the American method. The calculations of the American method are made by Paterson-Parker's rules.

Varicella Pneumonitis. Z. F. Endress and F. R. Schnell. Radiology **66**:723-726 (May) 1956 [Syracuse, N. Y.].

A 32-year-old woman had contracted chickenpox from her daughter. At the onset of her illness four days before hospitalization, she had experienced a sore throat coincident with the rash and a hacking cough. During the second and third hospital days, new lesions appeared on the skin and oropharynx, accompanied by increasing soreness of the throat and hacking cough, only partially controlled by medication. By the fourth day, the cough became almost constant. Multiple coarse and fine wheezes and rhonchi developed throughout the entire chest, together with fine crepitant rales and frank signs of consolidation at the left base. A chest film taken showed extensive inflammatory changes in all five lobes. The patient was placed in an oxygen tent and antibiotics were increased to 600,000 units of penicillin and 0.5 gm. of streptomycin twice daily. Gradual improvement followed and the patient was discharged from the hospital on the 14th day. The authors comment on pneumonia as a complication of chickenpox, pointing out that, although chickenpox is regarded as the mildest of the various exanthematous diseases of childhood, it can produce serious illness and even death. The incidence of complications at the present time is not known, but before the days of sulfonamides and antibiotics it was estimated at about 5%. Pneumonia was a complication in 21 of 2,534 cases of chickenpox reviewed in 1935, and 8 of these 21 cases were fatal, but microscopic examination revealed no evidence of virus pneumonia. Of the 18 cases of varicella pneumonia reported during the 15 years between 1940 and 1955, 7 had a fatal outcome.

Pneumonitis caused by the varicella virus is a rare but serious complication of chickenpox. Roentgenographically it produces a widely disseminated nodular infiltration involving all five lobes, with onset early in the second week of the illness. The lung infiltrates vary in size and shape; they are produced by confluence of numerous small areas of consolidation surrounding small foci of necrosis caused by the virus. Initial clearing is rapid and partial; subsequent regression is slow, a period of months elapsing before a normal appearance is finally reached. Clinically, severe dyspnea, cyanosis, and hemoptysis are commonly associated with the condition. Nephritis, encephalitis, hepatitis, pericarditis, orchitis, and laryngitis may accompany the pneumonia.

Surgical and Radiation Treatment of Carcinoma of the Breast: A New Concept. B. V. A. Low-Beer and H. G. Bell. Am. J. Roentgenol. **75**:1162-1168 (June) 1956 [Springfield, Ill.].

The existence of distant metastases is the problem in cancer of the breast from the moment the tumor is first recognized. It is obvious, therefore, that, in the treatment of cancer of the breast, when the aim is eradication of the disease, the problem is not whether simple mastectomy is preferable to radical mastectomy nor how radical a radical mastectomy should be. Neither is it fruitful to argue as to whether preoperative irradiation is to be preferred to postoperative irradiation. It is essential to realize that to limit treatment efforts to the primary lesion and to the first line of extension, i. e., axillary, mediastinal, subclavicular, and supraclavicular lymph nodes, is to espouse an entirely erroneous basic concept of the treatment that is doomed to result in failure in 90±3% of patients. Primary treatment of cancer of the breast must be directed not only to the local area of involvement but to any cancer tissue remote from the immediate region of the involvement.

Radiophosphorus (P^{32}) was, therefore, considered as a possible internal, selective, cancerocidal agent, and, since 1951, 80 women and one man have been treated with P^{32} in conjunction with surgery and regional roentgen irradiation. In 55 patients, the primary lesion was located in the outer half of the breast, in 14 patients in the inner half, and in 12 patients in and around the nipple. Seventy-four patients had radical mastectomy and seven had simple mastectomy. The postoperative staging was as follows: 30 patients with stage 1, 24 with stage 2, 22 with stage 3, and 5 with stage 4 carcinoma. Up to July, 1953 (22 patients), postoperative irradiation treatment including P^{32} was not started before the eighth postoperative day, and no patients with stage 1 carcinoma were included. Since September, 1953, all patients with carcinoma of the breast, including stage 1, have been treated by surgery combined with internal and external irradiation therapy, and the first dose of P^{32} has been administered to the patient on the operating table, as soon as the definite diagnosis has been made from a frozen section. Radiophosphorus treatment consisted of intravenous administration of from 20 to 30 μc of P^{32} per kilogram of body weight, and was given at intervals of two or three days until the bone-spleen-liver compartment daily dose reached a level of 15 to 20 gm. r/gm. This dose level was usually reached in from 14 to 20 days and was maintained by additional doses for another 10 or 12 days. The cumulative dose was estimated to be around 800 to 1,000 gm. r/gm. in the bone-spleen-liver compartment and around 75 to 100 gm. r/gm. in the soft tissue compartment. The total dose in millicuries varied between 12 mc. and 18 mc. in about 30 days, depending on the patient's weight. Simultaneous roentgen treatment consisted of irradiation of the axilla, the supraclavicular areas and the mediastinum with tissue doses in the range of 4,000 r delivered in 35 days.

Of the 22 patients treated with surgery in conjunction with roentgen rays and P^{32} between July, 1951, and July, 1953, five (two with stage 2 and three with stage 3) died. Of the 59 patients who were treated since July, 1953, one patient (stage 3) had died up to the time of the writing of the paper. In every patient treated with P^{32}, marked depression of all blood elements was observed by the end of the treatment course. Thrombocytopenia was particularly marked, but there was no obvious bleeding tendency. Within four weeks after the conclusion of the treatment, there was an almost complete recovery of the hematopoiesis. Patients over 70 years of age should be carefully selected for P^{32} treatment. It would be

premature to draw conclusions at this time with respect to the efficacy of the authors' method of treatment. Although this method cannot insure a 100% cure rate for cancer of the breast, there is every justification for a thorough exploration of its potentialities in the primary treatment of breast cancer.

The Danger of Cancer from Thorotrast as a Diagnostic Medium. E. Budin and J. Gershon-Cohen. Am. J. Roentgenol. 75: 1188-1193 (June) 1956 [Springfield, Ill.].

Thorotrast, a colloidal solution of thorium dioxide, is a radiopaque agent that is known to be radioactive and has been shown by experimental work to be carcinogenic. The American Medical Association Council on Pharmacy and Chemistry and other authorities have repeatedly warned against use of thorotrast because of this risk. Despite these facts, thorotrast is still used today for many diagnostic procedures in radiology, recommended in current medical literature, and advertised for multiple uses. The limited clinical evidence of its carcinogenicity is chiefly the result of the long latent period between the injection of thorotrast and the appearance of malignant changes. This accounts for the relatively few cases of malignancy so far reported. A direct cause and effect relationship is difficult to prove even when the malignancy develops at the precise site of residual retention. Two illustrative cases are described. In one of these, carcinoma of the breast occurred in a 43-year-old woman 17 years after thorotrast had been injected into the ductal system of the patient's right breast for roentgenographic studies followed immediately thereafter by the surgical removal of a fibroadenoma. Recent roentgenograms made during preoperative studies revealed changes suggesting the presence of a malignant lesion surrounding residual thorotrast. A radical mastectomy was performed, and roentgen examination of the biopsy specimen showed the major portion of the residual thorotrast concentrated precisely at the site of the tumor. The surgical specimen also revealed the presence of thorotrast in several axillary lymph nodes. An autoradiograph showed the tracks of alpha particles arising from the region of the malignant cells. The other case was that of a 65-year-old woman in whom a barium enema revealed a constricting lesion of the splenic flexure suggesting malignancy. Cancer appeared in the colon adjacent to the spleen, which was small and densely studded with opaque material. Residual thorotrast was suggested and confirmed both by a positive history of a thorotrast injection 16 years previously and by the histological appearance of the microscopic sections.

Thorotrast should not be used at all in patients for whom a satisfactory alternative is available, especially in such procedures as retrograde pyelography, arteriography, mammography, and myelography. The use of thorotrast in cerebral angiography should be sharply restricted, and the replacement of thorotrast in cerebral angiography by recently developed radiopaque agents should be accelerated.

ANESTHESIA

The Choice of Anesthetic Used in Cesarean Section: An Important Factor in Maternal and Fetal Prognosis. A. Russo and I. Volpi. Minerva ginec. 8:197-214 (March 15) 1956 (In Italian) [Turin, Italy].

The authors discuss the choice of anesthetic to be used in cesarean section in relation to the maternal and fetal prognosis. Ether narcosis is good for the mother and not for the fetus. Ether narcosis mixed with gas is good for both. Spinal anesthesia is the least dangerous, but its indications are difficult to determine. It is useful when the clinical status of the mother is good and the cesarean section is performed for the benefit of the fetus. Spinal anesthesia can be used in patients with disease of the respiratory system or with acute and normotensive toxemia. It is not indicated for patients with chronic hypertension and heart disease. They should receive local anesthesia, which is also indicated for patients with diabetes and preeclampsia. Local anesthesia is always better for the fetus. The treatment of 329 babies born by cesarean section is discussed. A first group of 69 patients was studied from 1940 to 1948. A second group of 260 patients was studied between 1949 and 1954. In the first group, ether narcosis was used in 59.4% of the cases. In the second group, spinal anesthesia was used in 48.4% of the cases and mixed narcosis in 31.1%. The mortality rate of mothers was 2.8% in the first group and 0.38% in the second. The anesthetic per se was never fatal. The mortality rate of the babies was 2.8% in the first group and 1.1% in the second. Narcosis with barbital was fatal in 4.7% of the cases, mixed narcosis in 2.4%, ether narcosis in 2.3%, and spinal anesthesia in 0.79%. Other types of anesthesia were not fatal. Ether anesthesia was associated with the highest frequency of reanimations: 12.1% in the first group and 7.1% in the second. Spinal anesthesia, on the other hand, was associated with the lowest frequency: only 5% of the cases.

PHYSIOLOGY

The Effect of Glucagon on Carbohydrate Metabolism in Normal Human Beings. P. K. Bondy and L. R. Cardillo. J. Clin. Invest. 35:494-501 (May) 1956 [New York].

Since the isolation of glucagon (hyperglycemic-glycogenolytic factor) from the pancreas and the demonstration that it is released in appreciable amounts into the blood stream, there has been much speculation about the possibility that diabetes mellitus may result from an imbalance between secretion of insulin and glucagon. The present investigation was undertaken to discover whether glucagon could produce an elevated blood glucose concentration with inhibition of glucose utilization, since this combination is usually observed in diabetic patients. The authors gave glucagon intravenously to normal human subjects. It produced a rapid rise of arterial and venous blood glucose concentrations, with increased arteriovenous glucose differences. No change in peripheral blood flow occurred. When given by constant intravenous infusion for two hours, glucagon caused a rise of both arterial and venous glucose concentrations with increasing arteriovenous glucose differences for about one hour, after which the arterial glucose level fell. Toward the end of the test period hypoglycemic symptoms often occurred. The falling glucose concentration could not be prevented by larger doses of glucagon. Over the two-hour period serum inorganic phosphate and plasma and whole blood alpha amino nitrogen concentrations fell steadily. There was no change in blood ketone body concentration. In all respects, the effects of glucagon were similar to those of doses of glucose that produced comparable arterial glucose concentration curves and different from those of growth hormone. These observations give no support to the concept that glucagon is diabetogenic, since no evidence was obtained of reduced glucose utilization. It is more likely that, in the intact organism, glucagon works synergistically with insulin to release glucose from the liver, thus making it available for the peripheral utilization promoted by insulin.

Effects of Dividing the Pituitary Stalk in Man. D. S. Russell. Lancet 1:466-468 (April 21) 1956 [London, England].

The author calls attention to the divergent results of dividing the pituitary stalk during intracranial operations. On the basis of three case histories she attempts to reconcile these divergent results in the light of recent investigations on the intimate vasculature of the pituitary body. In the first two patients, necrosis of the anterior lobe resulted from the operative division of the pituitary stalk. In the third patient a similar necrosis was induced by carcinomatous permeation of the portal vessels. Acute deficiency of the anterior lobe preceded death in all three cases, the length of survival being similar in the two who did not receive hormone therapy. None of the three patients had any evidence of diabetes insipidus. It is recognized, however, that an intact anterior lobe is essential to the development of this syndrome, though precisely how this operates is controversial. Observations on the third patient demonstrated the essential part played by the portal vessels of the stalk in maintaining the nutrition of the anterior lobe. The extent to which necrosis of the anterior lobe results seems to depend directly upon the completeness with which the portal vessels are interrupted and hence on the level of division. It is suggested that division of the stalk at its junction with the gland may be as effective clinically as total hypophysectomy.

BOOK REVIEWS

Textbook of Medical Physiology. By Arthur C. Guyton, M.D., Professor and Chairman of Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson. Cloth. $13.50. Pp. 1030, with 577 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C.2, England, 1956.

Attractive in outward appearance, this book proves on reading to be equally engaging in content. Intended for the use of medical students in their physiology courses, it gives the essentials of each subject in a forthright, concrete, and unaffected manner that should be appreciated equally by the neophyte and by the mature reader. Physicians prescribing anticoagulants, relaxants, and diuretics wish occasionally for a book that will bring them up-to-date on the fundamentals of such subjects as blood-clotting, feed-back mechanisms in the brain, and reabsorption in the kidney. For this purpose they should find this book excellent. In addition to the author's pleasing style, the arrangement of the pages, especially the use of the double column, appeals to the eye and helps to keep the reader oriented. The divisions of physiology are taken up in the following order: cellular physiology; nerve and muscle; circulation; body fluids and the kidneys; hematology; respiration; neurophysiology; special senses; digestion, metabolism, and energy; endocrinology, including reproduction; and radiation. There is a judicious use of illustrations. Each chapter ends with an adequate bibliography, and the index is good.

The misgivings expressed in the preface in regard to the advisability of a "one-man attempt to write a physiology text" are forgotten as one proceeds through this well-integrated book that shows such a balanced command of the entire field. Various items will need future attention. An important one is the pulmotor, the dangers of which are set forth on page 444. This expresses the attitude inculcated in the United States by the late Yandell Henderson, who was imbued with a great fear of overventilation and acapnia. His attitude was not shared by European physiologists, who continued to gather data on safe limits for positive and negative pressures for devices of this kind and were not afraid to apply them. Henderson's fear of overventilation resulted in continued use of Schafer's prone pressure method in the United States long after it had been abandoned in various European countries in favor of the more effective Holger Nielsen method. This latter has now been adopted here, and it is described in this book appropriately as the back-pressure arm-lift method. It is to be hoped that the paragraphs on the pulmotor will be correspondingly modernized in a future edition. The section on physiological optics can be made more helpful by adding details about the reduced or schematic eye, especially the concept of the nodal point. On page 23 the word "undamped" would be clearer than "driving" as applied to various kinds of oscillations. There is much in this book to remind one of the great Landois-Rosemann "Physiologie des Menschen," a one-man attempt that has continued through 26 editions. It is to be hoped that the author of the present work will be able to continue similarly, perfecting and polishing his book into something equally magnificent.

The Laboratory Diagnosis of Coagulation Defects. By Pietro de Nicola, M.D., Associate Professor, Department of Internal Medicine, University of Pavia, Pavia, Italy. Publication number 269, American Lecture Series, monograph in Bannerstone Division of American Lectures in Pharmacology. Edited by Chauncey D. Leake, Ph.D. Revised translation of La diagnosi dei difetti di coagulazione, Biblioteca Haematologica, Pavia, 1954. Cloth. $7.50. Pp. 240, with 62 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

This book is based on the author's experience, first as assistant to Prof. Paolo Introzzi at the University of Pavia and later in the United States during the tenure of a United States government fellowship administered by the Institute of International Education. It is a revised translation from Italian. Spanish and German editions have appeared or are in progress. Several books dealing with disturbances of hemostasis have appeared recently. This one is an attempt to present a condensed summary of essential current knowledge of this highly controversial and largely incomplete subject. In the first of five chapters on physiological background, the new concepts of blood coagulation and the various factors involved are discussed. Chapter 2 deals with the general diagnosis of coagulation defects. This is elaborated in greater detail in chapter 3, on the special diagnosis of such defects. Here each known abnormality is analyzed with the help of up-to-date information and methodology. The technical section in chapter 4 gives a brief and well-organized outline of the equipment, standard solutions, and reagents required in practically all modern techniques. The last chapter is entitled Conclusions, although actually it is a summary of the factual information presented in the preceding pages.

The main feature of the monograph is its brevity. In a field as complex and unsettled as blood coagulation, brevity may not be so much a blessing as in a more settled area of our knowledge. The advanced student of the subject will find in the book a valuable and interesting condensed version of the current status of technical aspects of the laboratory diagnosis of coagulation defects. The beginner should also profit and be stimulated, but he may also be misled by a tendency to oversimplification, especially in the technical section. Some procedures are made to appear much simpler and less time-consuming than they are. There are occasional inconsistencies, such as the statement on page 14 that "PTA is not adsorbed with barium sulphate and other adsorbents," whereas in table 7 it is listed as being adsorbed. On page 98, k and ma values are discussed but are not explained there or elsewhere. A few examples of defective translation (the translator is not named) were noted: "It has been assumed that clot retraction takes place also in vivo, in correspondence of intravascular clots" (p. 33). "The values are less and less reproducible the longer become the clotting times" (p. 47). "This finding is observed only in a few cases, partly because of technical reasons, and also for theoretical implications" (p. 71). There is also much evidence of careless proofreading. These defects add to the difficulties already inherent in the subject matter and detract from the usefulness of the book. It is not a book for the uninitiated, nor is it "suitable for . . . exact information," as stated in the preface.

Tumors of the Skin. By Herbert Conway, B.S., M.S., M.D., Professor of Clinical Surgery, Cornell University Medical College, New York. Publication number 270, American Lecture Series, monograph in Bannerstone Division of American Lectures in Surgery. Edited by Michael E. De Bakey, M.D., Professor of Surgery and Chairman of Department of Surgery, Baylor University College of Medicine, Houston, Texas, and R. Glen Spurling, M.D., Clinical Professor of Surgery, University of Louisville, Louisville, Ky., Plastic Surgery Division. Editor: James Barrett Brown, M.D., Professor of Clinical Surgery, Washington University School of Medicine, St. Louis. Cloth. $13.50. Pp. 267, with 178 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

This monograph presents a thorough and detailed consideration of the clinical characteristics, growth factors, frequency of occurrence, and surgical methods of treatment of cutaneous tumors. Each tumor is described briefly, yet succinctly, with the intent that the monograph should function as a useful reference. Following the discussion of the individual tumors, there is a short but adequate bibliography. Artists' sketches of techniques of operation are used as a guide to experienced surgeons who may be called on to use the methods of plastic surgery in the management of tumors of the skin. They are not intended to teach surgery to those who are not trained in this field. So much emphasis is placed on surgical treatment that the book should have been called "The Surgical Management of Tumors of the Skin." The author believes that, with rare exceptions, all types of cutaneous tumors should be removed surgically. This tenet disregards the extensive experience of dermatologists and others

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

responsible for the treatment of such lesions. Dermatological procedures for the removal of a xanthoma, papilloma, adenoma sebaceum, or of other benign lesions are equal, if not superior, to the techniques advised in this volume. On page 163 the author states: "Electrodesiccation has been rather commonly used for destruction of both benign and malignant skin lesions. It is mentioned only to be condemned." Further on, the qualification is added that it may be used in the treatment of warts. Most dermatologists, radiotherapists, and other practitioners of medicine who have had vastly greater experience than the author with this and other nonsurgical techniques will not agree. The only nonsurgical procedure discussed in detail in this volume is the author's technique for tattooing port wine stains. These criticisms are minor, though, for the book is a lucid and thorough exposition of both simple and advanced surgical forms of management of skin growths. The print is clear; the photographs are excellent. This monograph is a valuable contribution, and it is recommended to all physicians concerned with the management of cutaneous tumors.

Immunity. By Hideo Moriyama. Cloth. $5. Pp. 203, with 16 illustrations. Shonan Hygiene Institute, Kamakura; sole agency: Igaku-Shoin Company, Ltd., 20, Hongo-6, Bunkyo-ku, Tokyo, Japan, 1955.

The book is divided into two parts, each with its own bibliography. In the first part, entitled Principles of Immunity, the author endeavors to develop his theory concerning the nature of antibodies and the relationship between antibodies, enzymes, and viruses. In the second part, entitled Immunological Reactions, the author considers specific immunologic reactions, such as the precipitin reaction and complement fixation, and attempts to explain these in the light of the theories he has advanced in the first part. The book is essentially a speculative treatise on the basic aspects of immunology. Specific diseases are not considered. The author has read widely and thought a great deal about the ultimate basis for immunologic reactions. Although his views are interesting and may be correct, it should be fully realized that they are oftentimes speculative and not factually substantiated. Essentially, the author believes that all immunologic reactions derive from structural changes in proteins. The book endeavors to explain how these changes could be brought about and how certain specific immunologic reactions can be interpreted in the light of such a thesis. The book is a sister volume to a work called "The Nature of Viruses and the Origin of Life." A minor weakness is that occasionally the reader is referred to the other volume for an explanation. The book is definitely not for a beginner in immunology, such as a medical student or a beginning graduate student; nor is it a work for the average practicing physician who wants a reference book from which he can obtain explicit data concerning specific immunologic reactions. The book should be of interest to the advanced student in the field who wishes to get a slightly different point of view. He will find that the author has gathered points from many ancillary fields in an endeavor to support his thesis. The text suffers from many minor typographical errors, such as the misspelling of names. These are quite numerous, but in no case is the meaning obscured because of them. The English is good, although there are occasional nonidiomatic phrases; but these do not cause confusion.

Noradrenaline: Chemistry, Physiology, Pharmacology and Clinical Aspects. By U. S. von Euler, M.D., F.A.C.P. (Hon.), Professor of Physiology, Faculty of Medicine, Karolinska Institut, Stockholm, Sweden. Publication number 261, American Lecture Series, monograph in Bannerstone Division of American Lectures in Physiology. Edited by Robert F. Pitts, M.D., Ph.D., Professor of Physiology and Biophysics, Cornell University Medical College, New York. Cloth. $11.50. Pp. 382, with 88 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

This book summarizes current information concerning the chemistry, physiological effects, pharmacology, and clinical significance of levarterenol (*l*-norepinephrine) bitartrate. In 1946 the author first presented evidence that levarterenol was the major pressor amine involved in the chemical transmission of adrenergic nerve impulses. Over 700 references are included in the bibliography, and numerous excellent illustrations are presented. A minor defect is the wide use of the initials A and NA for epinephrine and *l*-norepinephrine respectively. The highly technical nature of the book will probably appeal to the research worker rather than to the clinician, but the latter should find several chapters, particularly those devoted to the association of levarterenol and pheochromocytomas and to the therapeutic uses of levarterenol, of great interest.

Diseases of the Endocrine Glands. By Louis J. Soffer, M.D., F.A.C.P., Clinical Professor of Medicine, State University of New York, College of Medicine, New York City. With J. Lester Gabrilove, M.D., F.A.C.P., Assistant Attending Physician, Mount Sinai Hospital, New York. Section on Gonads by Arthur R. Sohval, M.D., F.A.C.P., Associate Attending Physician, Mount Sinai Hospital. Second edition. Cloth. $16.50. Pp. 1032, with 105 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1956.

This edition has omitted the section dealing with carbohydrate metabolism and diabetes mellitus in order to keep the volume within a reasonable length and because this subject needs separate treatment due to its complexity. Section 1 deals with the hypophysis, section 2 with the adrenals, section 3 with the gonads (including a special chapter on the virilizing syndrome), section 4 with the thyroid, and section 5 with the thymus and parathyroids. There are no chapters 30, 31, 32, 33, or 34 (no break in the page numbers, however), and chapter 35, the appendix, is devoted to a detailed description of laboratory tests of endocrine function. It appears to be complete and accurate. The book is well written and has a voluminous bibliography. One minor criticism would be the amount of space devoted to case histories. The book should be a worthwhile addition to the library of any endocrinologist.

Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery & Radiology. By John Caffey, A.B., M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University, New York. Third edition. Cloth. $28. Pp. 1059, with 1267 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

This book has long since established itself as a classic in the field of diagnostic pediatric roentgenology. The new edition is more complete than ever, containing 197 more pages and 383 new illustrations. The subject matter has been expanded to keep abreast of the newer developments, advances, and procedures. As in the past, the author stresses the normal and the variants of normal at various ages, which is particularly important in this field of roentgenology. A new section on congenital dysplasia and dislocation of the hip has been added. Many other new subjects are included, and previous sections have been enlarged and rewritten with additional illustrations. This book truly represents one of the best and most informative works dealing with roentgenology ever published. It is a real classic not only for radiologists but for any one in any specialty interested in the diagnosis and treatment of diseases in children. It is recommended without reservation.

Preparing for Motherhood: A Manual for Expectant Parents. By Samuel R. Meaker, M.D. Cloth. $2. Pp. 196, with illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

The first chapter of this book emphasizes our modern philosophy that having a baby is a family affair and that education concerning pregnancy and labor concerns the husband as well as the wife. An intelligent, well-informed father will make the birth of his child a wonderful experience and may save the physician much grief. The story of human reproduction is told in a friendly and informative manner. The readers are told about the signs and symptoms of normal pregnancy as well as some of its complications. Prenatal care in all its aspects is discussed, and many questions that inevitably arise in the course of pregnancy are answered. Experiences in the hospital, pain relief and anesthesia, and the feeding of the newborn infant are presented; throughout the book the author emphasizes the fact that knowledge and understanding are important ingredients in the preparation of the mother for childbirth. The book is illustrated by a few simple drawings, which make the text more interesting.

QUERIES AND MINOR NOTES

UNHEATED FORMULAS FOR INFANT FEEDING

To the Editor:—*Please discuss briefly unheated formulas for infants. I refer to formulas that have already been sterilized and refrigerated and that are then given ice-cold from the refrigerator.* *J. P. Gibson, M.D., Abilene, Texas.*

Answer.—The reasons for heating infant milk mixtures have more weight in their favor than mere convention or propriety. First, it is a proved physiological fact that ingestion of food at less than body temperature delays the emptying time of the stomach, emptying time per se being an accepted digestive index of any food. Secondly, optimum ptyalin (starch enzyme) and rennin and pepsin (casein enzymes) activity, which occurs in the stomach, is known to require body temperatures (98.5 F or 37 C) in vivo and in vitro. The third reason as it pertains to infants is that before gastric digestion can begin the stomach contents must assume body temperature. When this is required of cold food in the stomach, the heat is derived from the infant's gastric circulation by conduction and radiation, and hence from general body heat. Thus, caloric energy otherwise used by the infant for anabolic processes is sacrificed. In premature or clinically immature infants, this process would be a useless dissipation of energy by an organism with already well-known problems of thermal control and weight-gain. In some unpublished observations made by Brennemann relative to his well-known curd studies in 1920, it was observed that milk mixtures given at room temperatures (72 F or 22 C), remained in the stomach as long as five hours after ingestion. The identical mixtures given at body temperatures left the stomach in three to three and a half hours. No observations were made of milk at refrigerator temperatures (milk in the average home refrigerator is about 40 F or 5 C), but it may well be postulated that such milk would delay gastric emptying time as long as, or p.rhaps longer than, five hours. However, much more is made of warming infant formula mixtures than is warranted by factual needs. Many baby attendants have a fetish of heating baby milk foods, using the time-honored "milk-on-the-wrist test," which, to even feel the warmth of the milk by this method, would achieve a milk-in-bottle temperature of at least 120 F or 49 C. The efficacy of the colloquialism that hot milk "will warm up the baby" is open to debate, since infants have not lived long enough to be impressed by the psychological effect of the warming possibilities of hot food, erroneously so inferred by adults. Nature's guide of human milk, excreted at 98.5 F or 37 C to the nursing breast-fed infant, would seem to make this a likely temperature for optimum gastric digestion and stomach emptying time.

AMPHETAMINE

To the Editor:—Does amphetamine influence the mutation rates of micro-organisms? I saw a remark in Annual Review of Physiology *that chemicals that produce mutations are also carcinogens. Many doctors prescribe amphetamine as a weight reducer, as well as for narcolepsy. If this drug is a mutagen, and if this should imply action as a carcinogen, the organ on which this effect should be strongest would naturally be the stomach. Since this is also the commonest site of internal cancer in man, there might be some connection. Of course, amphetamine is a new drug and could not account for the prevalence of stomach cancer in the past.*

Alfred B. Mason, M.D., Camp Lejeune, N. C.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The correlation between carcinogenic and mutagenic activity is quite close. However, many carcinogens have failed to display mutagenic activity, while many mutagens have not been proved to be carcinogens. This, however, does not necessarily negate the hypothesis that cancer is a somatic mutation that can be brought about by substances that induce genetic mutations. Usually mutagenic activity is demonstrated in bacteria or insects, while carcinogenic activity is studied in mammals. Many species differences must, therefore, be taken into account, such as differences of penetration of the drug and the nature and speed of the detoxification. Thus, carcinogenic activity could be due to a metabolic breakdown product, or the toxicity of a known mutagen to higher animals might preclude satisfactory screening for carcinogenic activity. Reference could not be found for a mutagenic activity for amphetamine. However, the site of carcinogenic activity for a given drug cannot necessarily be predicted, since many carcinogens are remote-acting, inducing tumors in certain specific organs or tissues regardless of the route of administration.

Answer.—Concerning the inquiry relating to amphetamine-induced mutations and possible carcinogenic effects, the available literature has been reviewed and no reference to the influence of amphetamine on mutation rates in micro-organisms has been found. Inasmuch as the drug has been in widespread use for about a decade, it appears unlikely that it would have such an effect in man. It is believed that not all chemicals that induce mutations are also carcinogenic. Penicillin, for example, is known to cause mutagenic effects in certain unicellular organisms, but it never has been implicated as a human carcinogen. While the possibility exists that amphetamine can induce mutations in micro-organisms (and perhaps in man), the likelihood of carcinogenic effects by its clinical application is extremely remote.

SCHISTOSOMIASIS

To the Editor:—*Can estimates or prognoses be given regarding infestation with Schistosoma mansoni in young Puerto Rican males who are asymptomatic? These patients have rectal lesions and show slight elevation on the sulfobromophthalein dye test. How many of these patients would develop pipe-stem cirrhosis? Is there any way to gauge the amount of infestation, i. e., heavy or light? Most of these Puerto Ricans have been away from their island for several years. Without further treatment does the adult fluke die out over a period of years? Does treatment with antimony potassium tartrate and Fuadin alter the pathological process in the intestine and liver at this stage, i. e., 5 to 10 years after the onset of infestation, or is the purpose of therapy a prophylactic means to avoid cirrhosis?* *Leonard Breslaw, M.D., Lewisburg, Pa.*

Answer.—Examination of Puerto Rican inhabitants in New York City, particularly children, indicates about 10 to 15% have Schistosoma mansoni. The majority of these individuals are asymptomatic, and it is not possible to estimate the percentage of infected individuals who will develop hepatic cirrhosis. It is difficult to determine the density or severity of infection because of the influence of the duration of infection on the number of eggs that escape into the intestinal tract. Thus in recent infections, where a large proportion of the eggs laid escape into the intestinal tract, one could determine relative densities of infection by quantitative egg-counting methods of stool examination. In relatively old infections of the same degree of severity few eggs might escape, and this would nullify the validity of the quantita-

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

tive stool egg count in relation to the severity of the infection. Live worms and viable eggs have been found in Puerto Ricans in New York about 20 years after their last exposure on their home island, indicating that the adult worms may survive and produce viable eggs for relatively long periods of time. The objective of specific treatment is to destroy the adult worms and thus prevent the progressive pathological changes in the gastrointestinal tract and liver and/or other organs that are the result of the presence of both the worms and the eggs. After specific treatment, reparative processes may completely obscure any irreparable pathological changes and organic function may be restored to normal levels. Progressive changes are stopped, and thus the effects of treatment are beneficial not only in relation to the cessation of immediate damage but also in the prevention of progressive disease.

PRECAUTIONS ON A TRIP TO AFRICA

To the Editor:—*Some suggestions were sent me about immunizations for our trip through Kenya, Tanganyika, Mozambique, and South Africa and two drugs were mentioned as preventing malaria, chloroquine and quinacrine. Atabrine has also been suggested to me. Which one would probably be best. Thirty years ago we went to the Far East and were told not to eat salads, berries, and uncooked vegetables. Would the same advice now be true in Africa?*

Robert W. Shearman, M.D., Brooklyn, N. Y.

Answer.—Chloroquine (Aralen) diphosphate is preferred over quinacrine for the suppression of malaria. Quinacrine is a synonym of Atabrine. Single weekly doses of 500 mg. of chloroquine diphosphate will produce complete suppression of all forms of malaria and will provide a suppressive cure of falciparum malaria. However, vivax and possibly malariae (quartan) infections will produce clinical attacks several weeks after termination of suppressive therapy. For this reason, it is advisable to continue such therapy until return to an area in which adequate diagnostic and hospital facilities are available. It is well to avoid the consumption of raw salads, berries, and vegetables in areas in which sanitation is at a low level, including most parts of Africa. Dangers of acquiring amebic infection from raw vegetables may be obviated to a considerable extent by soaking the vegetables in vinegar containing 5% acetic acid for at least 30 minutes at a temperature of 30 C (86 F) (Jones, M. F.: *Am. J. Trop. Med.* 1: 576-584 [July] 1952). It is advisable also to boil all drinking water or to employ one of the chlorine or iodine preparations for sterilization.

VAGINITIS IN DIABETIC PATIENT

To the Editor:—*Please send information on nonspecific vaginitis and vulvitis in a 24-year-old woman who has diabetes mellitus. She shows a definite glycosuria and a comparatively low blood sugar level, the highest being 180 mg. per 100 cc. Forty-six units of insulin keeps the blood sugar level down to about 80 mg. per 100 cc. and she shows about 1+ sugar in the urine. Any increase of insulin gives her an insulin reaction occasionally.*

M.D., Illinois.

Answer.—It is assumed that the blood sugar level of 80 mg. per 100 cc. is a fasting blood sugar level. It is possible, particularly if protamine zinc insulin is being used, that the blood sugar level before breakfast may be quite normal but may rise after meals to levels that permit glycosuria. It is suggested therefore that the blood sugar level be determined two or three hours after breakfast and two or three hours after lunch. If it is elevated at these times, and if protamine zinc insulin is being used, a change to isophane insulin might provide better control of the postprandial blood sugar level. If isophane insulin is already being used, the addition of a small amount of unmodified insulin, taken at the same time as the isophane insulin, would aid in keeping the postprandial blood sugar level more nearly normal. It is furthermore important to determine whether the urine is sugar-free after the evening meal. If not, a small dose of unmodified insulin before supper might be of help. The great majority of cases of vaginitis in diabetic women are caused by a mycotic infection. In such cases, the intravaginal instillation of Aci-Jel once or twice daily for several weeks is usually effective.

TUBERCULOUS PERICARDITIS

To the Editor:—*What is the treatment for hemorrhagic pericarditis that is tuberculous in origin? The patient is responding well to therapy with streptomycin, isoniazid, and aminosalicylic acid. However, there is some dispute as to dosage of streptomycin and also whether the pericardium should be excised to prevent late complication of constrictive pericarditis. The fluid is absorbing, and symptoms and signs of tamponade are diminishing.*

Morton J. Silk, M.D., Morris Plains, N.J.

Answer.—It is probable that prolonged treatment with combined dihydrostreptomycin and streptomycin, 0.5 gm. of each a day, plus 200 mg. of isoniazid, plus 12 gm. of aminosalicylic acid a day, will take care of tuberculous pericarditis and prevent constricting adhesions. Excision of the pericardium should be undertaken only after the acute pericarditis has completely subsided, as evidenced by a normal sedimentation rate, and then only if there are definite signs of constrictive pericarditis. Some new work has been done in France with the use of prednisone (Meticorten) in order to prevent fibrosis. The reports are favorable, but corticotropin, cortisone, and prednisone so frequently cause activation and spread of tuberculosis that this remedy seems very questionable. Intrapericardial injection of antituberculosis drugs does not seem indicated. If fluid collects in sufficient amounts to cause symptoms of pericardial tamponade, it should, of course, be aspirated.

PENICILLIN FOR ORAL USE

To the Editor:—*Please outline a dosage regimen on a weight basis for infants and children with reference to the use of phenoxymethyl penicillin orally.*

Richard M. Margolis, M.D., Charleston Heights, S.C.

Answer.—Phenoxymethyl penicillin (V-Cillin, Pen-Vee-Oral) is a new kind of penicillin for use orally. It exhibits a high degree of stability in the presence of gastric acidity. Because of this unique characteristic, antibiotic loss in the stomach, normally anticipated with penicillin G, does not occur; therefore, more penicillin is available for absorption. Blood levels ranging from 50 to 100% higher than those obtainable with comparable doses orally of penicillin G have been demonstrated clinically. Penicillin, like other antibiotics, should never be prescribed promiscuously. Some individuals are allergic to the first dose, while others become sensitized by repeated use; deaths have been reported occasionally, especially after penicillin given parenterally. Penicillin orally is for the treatment of infections known to respond to penicillin therapy, particularly those caused by Streptococcus, pneumococcus, Micrococcus, or gonococcus organisms. The dose, regardless of age or body weight, is usually 125 to 250 mg. three times daily, or every eight hours, in 125-mg. and 250-mg. capsules. It can also be given in pediatric suspension (V-Cillin pediatric or Pen-Vee suspension),—1 teaspoonful (125 mg.) every six to eight hours.

POSSIBLE HAZARDS IN RETREADING TIRES

To the Editor:—*Is the chemical ordinarily used in recapping tires a causative factor in leukemia? Is work of this sort considered an industrial hazard?*

George R. Wilkinson, M.D., Greenville, S. C.

Answer.—An automobile tire to be retreaded is first ground mechanically to evenness and then coated liberally with a rubber cement. Thereafter, strips of rubber are affixed to the glued surface and vulcanization is brought about. The rubber cement could be the present offender. Some such cements contain benzene, often called benzol. Evaporation from the tire surface affords abundant exposure in the absence of protective measures. Leukemia is not a characteristic response to benzene. Leukopenia is the common manifestation. There are now on record 14 instances of leukemia attributed to benzene action. Analysis of the cement will establish if benzene is a constituent. Air analyses of the workroom atmosphere during exposure may

reveal benzene. A simpler procedure is to examine the urine of workers lately exposed for the sulfate index. Recent exposure to benzene but not benzene poisoning thus may be established. Regardless of the presence of benzene in the cement, the process of tire capping or retreading may introduce exposures to dermatitis from diverse rubber accelerators and antioxidants and possibly from hydrocarbons other than benzene in the cement.

CALORIES IN CORNBREAD

To the Editor:—*An obese man now reducing his weight likes "cornbread" prepared by mixing cornmeal and water and frying it in bacon grease. How many grams of carbohydrate, protein, and fat and how many calories are in each cupful of cornmeal used in making this "cornbread?" How many grams of carbohydrate, protein, and fat and how many calories are in the 2 teaspoonfuls of bacon grease or vegetable shortening used to grease the pan in which the bread is fried?*

M.D., Georgia.

Answer.—The following table is from "Food Values of Portions Commonly Used" (Bowes and Church, Philadelphia, College Offset Press, Inc., 1954).

Food Values in Cornmeal and Fat

	Amount	Calories	Protein, Gm.	Carbohydrate, Gm.	Fat, Gm.
Cornmeal enriched, dry	1 cup	544	11.8	117.6	1.8
Bacon fat	2 teaspoons	84	...	0	9.3
Total		628	11.8	117.6	11.1

TREATMENT OF PYODERMA

To the Editor:—*Is it advisable to use Terramycin ointment or powder for skin infections before culture and sensitivity studies have first been made? Is the incidence of skin sensitivity due to the topical use of this antibiotic of sufficient magnitude to preclude its use routinely? How do Aureomycin, Terramycin, Achromycin, Furacin, bacitracin, and penicillin range in order of their sensitizing potency on skin?*

Milton Jabush, M.D., Lakewood, N. J.

Answer.—Theoretically and ideally the proper procedure to follow in the treatment of pyoderma would be to conduct culture and sensitivity tests, but such studies are time consuming, so that the usual procedure, which has proved to be practical, is to employ an antibiotic agent (as an ointment and/or systemically) first. If the infection is not controlled quickly, then sensitivity tests are made. Penicillin and Furacin are generally thought to be the most likely to sensitize the skin, bacitracin the least likely, and the others in between. The better course is to employ as a topical agent one, such as bacitracin, that is not likely to be used systemically.

AIDS TO ESTABLISH AUTOMATIC MICTURITION

To the Editor:—*Is there any apparatus available, such as a chair or its equivalent, that will aid in the development of an automatic bladder in a paraplegic female?* *M.D., Texas.*

Answer.—There are no mechanical devices yet developed to aid in establishing automatic micturition. Some success in voiding at predictable intervals may be obtained by a quantitative regulation of fluid intake to correspond with periodic attempts at voiding. This regimen, however, is usually only applicable to lower motor neuron lesions, where micturition may be initiated by straining and sustained by Credé's method. For techniques, consult "A Bladder and Bowel Training Program for Patients with Spinal Cord Disease," by Buchwald, McCormack, and Raby (Rehabilitation Monograph 3, New York, Institute of Physical Medicine and Rehabilitation, New York University–Bellevue Medical Center). Upper neuron lesions resulting in the so-called spastic reflex type of detrusor urinae frequently defy any efforts at training and usually require a permanent indwelling catheter in the female.

BOILING TAP WATER

To the Editor:—*What changes are made in boiling ordinary city tap water, where chlorine and fluorine are used in it? Does the boiling entirely get rid of the chlorine and fluorine? Is softened water healthy to drink?*

E. L. Cavenee, M.D., Champaign, Ill.

Answer.—Fluorine as such is not present in drinking water. The fluoride ion is naturally present in many waters and is added to some to aid in reducing dental caries. Boiling does not remove the fluoride ion. Boiling does remove chlorine when present as "free" chlorine ($HOCl$ or OCl^-) but has little effect on combined chlorine such as chloramines. There is nothing harmful per se about softened water or naturally soft water. Millions of people in the United States drink either naturally soft or softened water. The healthfulness of the water depends on other constituents than those responsible for hardness.

PORTAL HYPERTENSION

To the Editor:—*What are the accepted surgical methods of treating portal hypertension and ascites resulting from hepatic cirrhosis?* *M.D., New York.*

Answer.—At present, the two most commonly employed surgical procedures in the alleviation of the sequelae of portal hypertension are the direct portacaval anastomosis and the splenorenal shunt. Of the two procedures, the direct end-to-side portacaval shunt is preferred, if the situation permits. Portacaval shunting is contraindicated in patients with unstabilized ascites. Even when ascites is stabilized, shunting should be delayed further when the sulfobromophthalein retention is 35% or higher (after one-half hour); serum albumin, 3.5 gm. per 100 cc. or lower; serum bilirubin, 1.5 mg. per 100 cc. or higher; prothrombin time levels, 5 seconds or more above central levels; and cephalin flocculation, 3 to 4 +.

CENTRAL VISUAL FIELDS

To the Editor:—*What information is obtained in doing central visual fields at 1 and 2 m. with the same size test objects and also with a larger test object at 2 m.?* *M.D., New York.*

Answer.—At 2 m. a given test object will subtend a smaller visual angle than it will at 1 m. Therefore, it becomes a weaker stimulus to the patient's eye. By this means it is possible to outline a more subtle relative field defect. At a distance of 2 m., utilizing larger test objects to offset the decrease in stimulus due to the added distance, a larger projection of the field pattern is obtained on the screen. This permits a more accurate outline of the visual field, which may be especially valuable in mapping small defects. Also, it is possible to test the patient's reliability with this variation, since the change in the field size is predictable. An example would be "tunnel" vision in hysteria, which typically remains unchanged when the test distance is modified.

MYOCARDIAL INFARCTION

To the Editor:—*In a man 34 years of age who had died in his sleep, a small acute myocardial infarction was demonstrated. His health had been good except for a cold for three days, for which it is believed he was taking Neohetramine tablets. Would this drug have any bearing on his death?*

Charles F. Gaylord, M.D., Staunton, Va.

Answer.—There is no reason for an antihistamine to produce a myocardial infarction by itself. However, large doses of potent antihistamines have been known to produce cardiac stimulation, resulting principally in tachycardia. It is conceivable, although rather unlikely, that such cardiac stimulation in a damaged heart might result in a coronary occlusion. What makes it even more unlikely in this case is that Neohetramine is among the least potent and least toxic of the antihistamines.

PROTECTIVE COVER FOR WRIST WATCHES

To the Editor:—*Please name a protective cover for wrist watches to make them safe for wear by persons with skin very sensitive to the metal of the case.*

M.D., New York.

Answer.—It is possible to obtain leather, cloth, or other fabric cases for wrist watches. A simple method of solving this problem is to cover the back of the watch with adhesive tape. Another simple method is to treat it with collodion or colorless nail polish.

DRUGS THAT COLOR THE URINE

To the Editor:—*What drugs are capable of producing abnormal coloring in the urine?*

M.D., New Jersey.

Answer.—Drugs that produce abnormal coloring in the urine include trinitrophenol, reddish brown; phenols, brownish-black; pyridium, reddish-orange; aminopyrine, occasionally red; quinacrine, intense yellow; phenothiazine, red; methylene blue, green; and senna, rhubarb, cascara, aloe, santonin, and phenolphthalein, which color acid urine yellowish-brown and alkaline urine reddish or violet.

ARMY PERSONNEL "GASSED" DURING WORLD WAR I

To the Editor:—*The following additional published and unpublished data may be of interest concerning a query entitled "Army Personnel 'Gassed' During World War I" in* The Journal, *May 5, page 118. Case and Lea reporting the results of their study on the problem concerning British veterans found a statistically significant excessive liability to lung cancer for gassed British veterans (Mustard Gas Poisoning, Chronic Bronchitis, and Lung Cancer,* Brit. J. Prev. & Social Med. *9:62-72, 1955). It is of interest also that Yamada, Hirose, and Miyanishi (An Autopsy Case of Bronchial Carcinoma Found in a Patient Who Succumbed to Occupational Mustard Gas Poisoning,* Gann *44:216-218, 1953) observed the occurrence of lung and larynx cancers among Japanese workers employed in a war gas factory on Okuno Island. While the cited publication deals only with two cases of lung cancer, Yamada in subsequent observations found a third case of lung cancer and three cases of larynx cancer among members of this occupational group. The three cases of lung cancer were discovered at autopsy, while the three cases of larynx cancer were based on biopsy findings. Before the cancerous character of the respiratory diseases noted among these workers was correctly recognized, the diseases were known as "Okuno curse" and were clinically diagnosed as pulmonary tuberculosis, a diagnostic mistake repeatedly made and reported in the history of occupational cancers of the lung.*

W. C. Hueper, M.D.
National Institutes of Health
Bethesda 14, Md.

KRAUROSIS OF VULVA

To the Editor:—*In* The Journal, *May 5, page 117, is a question concerning kraurosis of the vulva. Apparently this question was referred to a gynecologist for answering. I believe that an entirely different answer would have been received had this question been referred to a dermatologist. Certainly kraurosis of the vulva is a dermatological problem in many instances. I would refer you to an article by Dr. Eugene P. Schoch Jr. and myself in* The Journal, *March 26, 1955, page 1102, in which we tried to point out that entirely too many vulvectomies are being done for noncancerous lesions. Certainly kraurosis of the vulva is a dermatological problem in process. It is an atrophic process. It is true that leukoplakia is very apt to appear on a kraurotic vulva. Even when this happens, it is a simple matter to use desiccation or some other means of removal of the leukoplakic spots. I believe that most dermatologists will agree that kraurosis vulvae will respond, in many cases, to dermatological therapy. Admittedly, in some cases of kraurosis vulvae, particularly in older women, vulvectomy is justified.*

C. H. McCuistion, M.D.
609 Capital National Bank Bldg.
Austin, Texas.

To the Editor:—*In Queries and Minor Notes, page 117, in* The Journal, *May 5, the answer on kraurosis of vulva deserves comment. Although the answer is extensive and covers various phases of the possible problem, one cannot tell whether the doctor asking the question or the doctor answering the problem are dealing with kraurosis vulvae or leukoplakia. Certainly the diagnosis, prognosis, and treatment for the two conditions are entirely different. Kraurosis vulvae is usually considered to be lichen sclerosus et atrophicus on the vulva, which is an atrophy of the dermis and epidermis. If the doctor is talking about a patient with kraurosis vulvae, the treatment suggested is far more radical than necessary, as kraurosis vulvae is a benign condition and not precancerous except when rarely complicated by leukoplakia. Leukoplakia is a hyperkeratosis of the epidermis and is definitely precancerous. Apparently the answer given applied to leukoplakia. I doubt very much if local medication is of value in either disease. It is time for practitioners, gynecologists, and others to be better informed concerning these two conditions. A well-performed biopsy would be diagnostic.*

Francis A. Ellis, M.D.
8 E. Madison St.
Baltimore 2.

SALIVARY FISTULA

To the Editor:—*I noticed the query regarding treatment of salivary fistula in* The Journal, *May 19, 1956, page 298. I successfully treated several cases with roentgen therapy when at the Cleveland Clinic. My first report was published in the* Annals of Surgery, *May, 1935. Reference is also made to this method of treatment on page 161 in the book "Clinical Therapeutic Radiology" (New York, Thos. Nelson & Sons), which I edited in 1950. I believe that, rather than attempting radical surgery, as suggested in* The Journal, *irradiation should be given a trial. The idea is to suppress the function of the gland. The dosage should be between 1,500 and 2,000 r given by protracted technique.*

U. V. Portmann, M.D.
721 N. Fourth Ave.
Tucson, Ariz.

FLIGHT AFTER PNEUMONECTOMY

To the Editor:—*The answer to a query in* The Journal, *March 31, 1956, page 1184, on how high a person may fly in commercial airplanes after a complete right pneumonectomy does not state that the mediastinum must become stabilized before any air travel is undertaken. Also, why pressurization of the cabin at 5,000 ft. is specified is not clear. I have data to prove that an adult can easily tolerate an altitude of 10,000 ft. with only one remaining lung, without difficulty. The usual commercial aircraft cabin can be pressurized to 8,000 ft. at an altitude of about 22,000 ft. Newer types of aircraft such as the Viscount can be pressurized to 6,000 ft. at 22,000 ft. In the last sentence of the answer the word should be "lower" not "higher." I might also add that the airlines carry patients with many types of medical conditions aboard regularly scheduled commercial aircraft.*

Ludwig G. Lederer, M.D., Ph.D.
Medical Director, Capital Airlines
Washington National Airport
Washington 1, D. C.